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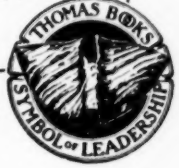

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A. M. A.
Archives of Neurology and Psychiatry

VOLUME 70 JULY 1953 NUMBER 1

PROGRESSIVE NEUROPATHIC (PERONEAL) MUSCULAR ATROPHY (CHARCOT-MARIE-TOOTH DISEASE)

Histological Findings in Muscle Biopsy Specimens in Fourteen Cases, with Notes on Clinical Diagnosis and Familial Occurrence

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AND
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OSLO, NORWAY

THERE seems to be a general feeling among neurologists that one is justified in considering as a disease entity the condition variously called "peroneal muscular atrophy of the Charcot-Marie-Tooth type," "progressive neuritic muscular atrophy," or "spinal neuritic form of progressive muscular atrophy." The weight of available evidence concerning its etiology, most recently reviewed by England and Denny-Brown,[1] is in favor of an affection of the spinal cord and of peripheral nerves being the primary process, the muscular changes being secondary; but few autopsy reports are found in the literature. However, biopsy of affected muscles may give information of interest, since it is now well established that the histological changes in the muscles in progressive muscular dystrophies differ in certain respects from those occurring in diseases involving primarily the peripheral motor neurons, such as amytrophic lateral sclerosis, progressive spinal muscular atrophy, syringomyelia, and poliomyelitis.[2] Brodal and Refsum [3] described

From the Neurological University Clinic, Rikshospitalet (Series 2, No. 200) and the Anatomical Institute, University of Oslo.

1. England, A. C., and Denny-Brown, D.: Severe Sensory Changes, and Trophic Disorder, in Peroneal Muscular Atrophy (Charcot-Marie-Tooth Type), A. M. A. Arch. Neurol. & Psychiat. **67**:1-22, 1952.

2. (*a*) Slauck, A.: Beiträge zur Kenntnis der Muskelpathologie, Ztschr. ges. Neurol. u. Psychiat. **71**:352-356, 1921; (*b*) Histopathologische Untersuchungen bei neuraler Myopathie, Klin. Wchnschr. **7**:2245-2247, 1928. (*c*) Wohlfahrt, S., and Wohlfart, G.: Mikroskopische Untersuchungen an progressiven Muskelatrophien unter besonderer Rücksichtsnahme auf Rückenmarks-und Muskelbefunde, Acta med. scandinav., Supp. 63, pp. 1-137, 1935. (*d*) Wohlfart, G.: Muscular Atrophy in Diseases of the Lower Motor Neuron: Contribution to the Anatomy of the Motor Units, Arch. Neurol. & Psychiat. **61**:599-620, 1949. (*e*) One of us (A. B.) has had the opportunity to confirm this in a rather extensive series of muscle biopsies from the two types of diseases.

3. Brodal, A., and Refsum, S.: Progressive Neural Muscular Atrophy (Charcot-Marie-Tooth): Case Report with Histological Examination of Excised Muscle, Acta psychiat. et neurol. **17**:99-122, 1942.

the findings in a clinically typical case of progressive neuropathic muscular atrophy of the Charcot-Marie-Tooth type and concluded that the muscular changes bore a striking resemblance to those in atrophies of spinal origin. Wohlfart[2d] corroborated these observations in another case. In some cases authors have found changes of the dystrophic type, but the clinical diagnosis in these cases was probably erroneous.[3]

On account of the scarcity of detailed studies of muscular changes in progressive neuropathic muscular atrophy, it was thought worth while to study more closely material collected for routine biopsy by one of us (A. B.) during the period from 1941 through the first half of 1952. The biopsy specimens were from patients treated in the Neurological University Clinic for progressive neuropathic muscular atrophy. Since it was essential to select only cases in which the disease could safely be classified clinically as progressive neuropathic muscular atrophy of the Charcot-Marie-Tooth type, as many patients as possible were reexamined clinically. In addition to the diagnostic control obtained by this follow-up study, new evidence on the familial occurrence of the disease was also produced, and will be reported in this paper.

MATERIAL AND METHODS

Altogether, 20 biopsy specimens of muscle in 14 cases in which the diagnosis of progressive neuropathic muscular atrophy was considered clinically certain form the material of the present study. The specimens were obtained with use of local anesthesia, care being taken to avoid infiltration of the piece to be removed. Most biopsy specimens were from the anterior tibialis muscle. It was attempted to have specimens from regions of the muscle affected by only moderate visible atrophy, since such regions might be expected to show the characteristic changes most clearly. After removal the biopsy specimens were placed for two hours in a gauze pad moistened with isotonic sodium chloride solution and then fixed in 4% formalin. After being embedded in paraffin, the blocks were cut at 15 or 10 μ. Some sections were cut in a plane parallel to the muscle fibers, and from the remaining part of the block a series of transverse sections were made. Some sections were stained with hematoxylin and eosin; others, by the Van Gieson method. When it proved desirable, additional sections were later made from the rest of the blocks. The findings are described and illustrated by camera-lucida drawings and photomicrographs and are summarized diagrammatically in Figure 4.

The selection of the cases utilized in the present study was made as follows: The records of all patients treated in the Neurological University Clinic in the period from 1941 to 1951, inclusive, under the diagnosis of progressive neuropathic muscular atrophy of the Charcot-Marie-Tooth type were examined. All cases in which there could be the slightest doubt about the diagnosis or in which there were concomitant diseases which might obscure the picture were excluded from the material. In the remaining cases, in which the diagnosis appeared conclusive, and in which biopsy specimens had been taken, the patients were called up for renewed examination at the Clinic or were examined by one of us (A. G. F.) in their homes. Except in six of the cases selected, a reinvestigation could be made. Because in many cases several years had elapsed since the patient had first been seen in the Clinic, many signs and symptoms had become more pronounced and served to corroborate the initial diagnosis. Furthermore, in one instance (Case 4) it turned out that since the patient had first been seen, nine years previously, two of her sisters had been taken ill with the same disease. (Unfortunately, muscle biopsies could not be done on these patients.) During the study an additional patient with progressive neuropathic muscular atrophy was admitted to the Clinic, in March, 1952, and his case is included in the material. Brief case histories of the 14 cases which form the material of the present study are given at the end of the paper.

DIAGNOSIS AND SYMPTOMATOLOGY OF PROGRESSIVE NEUROPATHIC MUSCULAR ATROPHY

The validity of any conclusions made from biopsy material is dependent essentially on a correct clinical diagnosis. Since several types of progressive neuropathic muscular atrophy have been distinguished in the literature, it is appropriate to give an account of the criteria on which the diagnosis has been based in the present study.

Charcot and Marie's [4] description, in 1886, of five cases and Tooth's [5] contemporary publication are the classic sources of information on the symptomatology of progressive neuropathic muscular atrophy. Charcot and Marie, as well as Tooth, emphasized the beginning of the muscular atrophy in the feet and legs, stating that usually only until several years later are the hands and arms affected. They also stressed the slow development of the disease, stating that the proximal parts of the extremities are relatively spared and that the muscles of the trunk, shoulders, and face are unaffected. Fibrillary twitchings (fasciculations) in the affected muscles are said to be common, as are vasomotor disturbances in the distal parts of the limbs. Cramps are common. Sensory disturbances, although usually absent, may occur, however, and may involve various sensory modalities. According to Charcot and Marie, the disease usually begins in childhood or early adolescence. It is commonly found to affect other children in the same family, and occasionally evidence of its occurrence among ancestors may be found. Later authors, studying this disease, have supplemented this classic description by the addition of particular features, but have chiefly produced evidence that its symptomatology, age of onset, and rate of progression may be more varied than is indicated in the classic descriptions. There is, however, no need to review the entire literature on progressive neuropathic muscular atrophy at this time, since we have confined our material to cases which may be considered typical.

As will be seen from the case reports (Appendix), the motor signs and symptoms observed in our cases conform to those described by Charcot and Marie and by Tooth. Thus, in all 14 cases the muscular atrophy started in the feet, and in 9 the hands were affected at a later stage. The atrophies progressed in a proximal direction. In several cases the characteristic circular border between atrophic distal muscles and better preserved proximal muscles was found. Examples are shown in Figure 1. Fibrillary twichings (fasciculations) in the affected muscles were observed in eight cases; in four others there were subjective signs which must be taken to betray the occurrence of fasciculations. In six cases there was a complaint of cramps.

With regard to other features, however, some of our cases differ somewhat from the classic descriptions. This applies particularly to the sensory disturbances and the age of onset of the disease. The principal points will be discussed briefly.

In 13 of our 14 cases, the disease was said to have begun at the ages of 1½, 7, 18, 22, 27, 29, 32, 35, 37, 38, 41, and 45. In one case (Case 14) the date of

4. Charcot, J. M., and Marie, P.: Sur une forme particulière d'atrophie musculaire progressive, souvent familiale, débutant par les pieds et les jambes, et atteignant plus tard les mains, Rev. méd. **6**:97-138, 1886.

5. Tooth, H. H.: The Peroneal Type of Progressive Muscular Atrophy, London, H. K. Lewis & Co., Ltd., 1886.

onset could not be determined. Thus, the majority of the patients had their first symptoms at a much later period of life than did those described by Charcot and Marie and by Tooth. However, several authors have made observations similar to ours. To cite only a few, Davidenkow,[6] in a large material, found 37 cases in which symptoms started after the age of 20, and in 4 cases even after the age of 50; in England and Denny-Brown's [1] extensive material the age of onset in some cases was also as late as 50. The latter authors emphasized that the disease tends to run a severer course when starting early in life. This conclusion seems to be supported by the findings in the present material. In this connection Case 14 is of some interest. When examined in 1944, the patient said that as long as he could remember the distal part of both calves had been unusually thin, but he

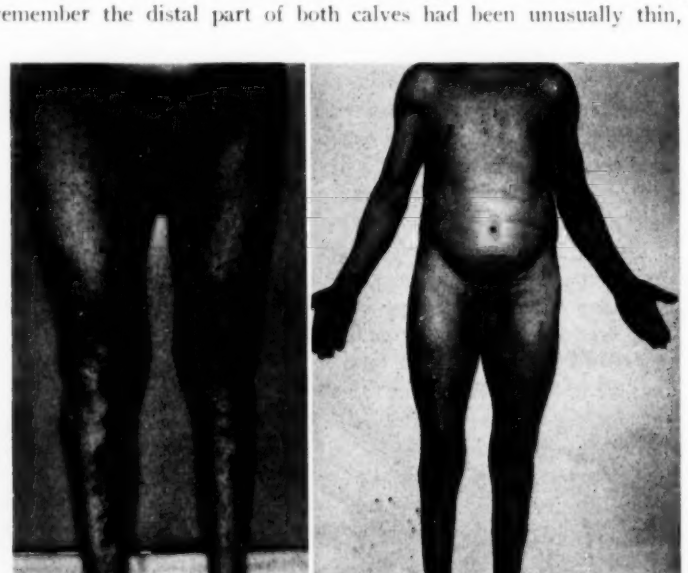


Fig. 1.—*A* (Case 11), age 55; duration of disease, 23 years. Marked atrophy of the left calf; some atrophy of the left thigh. Compare photomicrographs in Figures 8, 11, 12, 14, 17, and 25. Muscular changes were also present in right anterior tibialis muscle (Fig. 4).

B (Case 13), age 59; duration of disease, 37 years. Extreme atrophy of calves; considerable atrophy of the lower third of thighs; atrophy of right thenar muscles. Note signs of trophic disturbances in both calves and the pes excavatus. Compare Figures 4 and 9.

considered himself healthy and presented no signs of muscular weakness. Fasciculations, however, were present at that time, at the age of 64. Eight years later (1952) there was marked paresis of movements of his left foot, and hypesthesia and reduced vibratory sensibility were found distally in both legs. If only this patient had been seen, the diagnosis of progressive neuropathic muscular atrophy could have been made only with hesitation, but in view of the typical picture presented

6. Davidenkow, S.: Uber die neurotische Muskelatrophie Charcot-Marie: Klinisch-genetische Studien, Ztschr. ges. Neurol. u. Psychiat. **107**:259-320, 1927.

by his daughter (Case 10) this diagnosis may safely be made. This case appears to be one in which, at least at the beginning, the progress of the disease was extremely slow. However, the process must be assumed to have started before the age of 64, particularly in view of the presence of unequivocal histological changes seen in the muscle biopsy made at that time (Figs. 4 and 9). The rather advanced age at which many of our patients fell ill, therefore, does not contradict the diagnosis of progressive neuropathic muscular atrophy, the more so since for many of them (Cases 1, 3, 4, 5, 6, 7, 10 and 14) a familial occurrence supported the diagnosis.

Sensory disturbances were not found in all cases of the present series, and in none of them was there any severe impairment of sensation. In only two cases, however, were there no signs of this kind. Reduced cutaneous sensibility to various qualities was found in nine cases; reduced vibratory sense, in nine, and reduced joint sensibility, in one. Our findings are in agreement with the contention of Charcot and Marie that the sensory disturbances may affect different modalities but that they may also be absent. A similar wide variation was noted by England and Denny-Brown,[1] who in some of their cases found very marked sensory disturbances. As in their cases, the distribution of sensory changes in the present material frequently showed an approximately segmental pattern (see case reports). On the whole, it may be said that characteristic sensory changes when present support the diagnosis of progressive neuropathic muscular atrophy, but that absence of sensory impairment does not contradict the diagnosis; this is evident also from Pette's[7] review.

The many difficulties inherent in the determination of slighter sensory loss should be recalled. In the present material, the findings with regard to sensory disturbances supported the diagnosis in 12 cases, but the absence of sensory impairment did not invalidate the diagnosis in the 2 remaining cases. Similar considerations may be made with regard to the vasomotor disturbances, which were present in 8 of our 14 cases. It may be mentioned, also, that talipes cavus (pes excavatus) occurred in four cases.

In none of our patients could thickened peripheral nerve trunks be palpated. Although the hypertrophy of peripheral nerves may be extremely difficult to establish, it may at least be said that so far as this feature is concerned no evidence in support of the diagnosis of the progressive hypertrophic interstitial neuropathy of Dejerine and Sottas was found in our cases.

On the whole, we feel that the diagnosis of progressive neuropathic muscular atrophy in our cases is secure. In addition to the slowly progressive course and the signs and symptoms displayed, considerable emphasis must be laid on the familial occurrence in more than one-half the material.

FAMILIAL OCCURRENCE

As has already been mentioned, Patient 14, having a very moderate form of the disease, was the father of Patient 10, who was rather heavily affected. Patient 3 had a sister with the same disease, and his father most likely also had progressive

7. Pette, H.: Neurale Muskelatrophie, in Bumke, O., and Foerster, O., Editors: Handbuch der Neurologie, Vol. 16, Joseph, H., and others: Spezielle Neurologie VIII; Erkrankungen des Ruckenmarks und Gehirns VI; Angeborene, früherworbene, heredofamiliäre Erkrankungen, Berlin, Springer-Verlag, 1936, pp. 497-524.

neuropathic muscular atrophy. Patient 6 was a niece of Patient 7, whose father had muscular wasting and whose sister had been affected in a similar way. On Patients 2, 8, 9, 11, 12, and 13 no information of familial occurrence has been obtained, but, as is well known, negative evidence of this kind is not conclusive. The findings in the follow-up study of the patient in Case 4 are illuminating in this connection.

S. K. (Case 4) when treated in the Neurological University Clinic in 1943, knew of no cases of similar disease in her family. When she was seen again, in 1952, however, two of her sisters (G. H. B. and E. S.) had become affected with progressive neuropathic muscular atrophy, as verified by personal examination. Furthermore, she had obtained information that her maternal grandfather (O. G.) had probably had the same disease. The pedigree at the left in Figure 2 shows these relationships. Her mother (G. B.) died at the age of 38 and was not known to have presented any signs of muscular atrophy. Further study of the ancestors in Case 4 showed that the patient's grandfather's mother had a sister among whose progeny were four identified cases of progressive muscular atrophy, shown in the right half of the pedigree in Figure 2. Two of the affected members are A. S. and A. L. (Cases 1 and 5), respectively, of

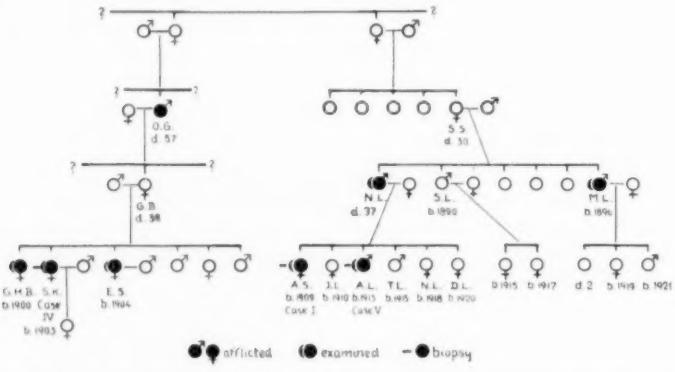


Fig. 2.—Pedigree of members of two families with progressive neuropathic (peroneal) muscular atrophy. In the legend below, *examined* means that the diagnosis was made in the University Neurological Clinic or by personal examination; when the year of birth (*b.*) but not the age at death (*d.*), is indicated below the symbols, the patient is still living.

this material; the two others (N. L. and M. L.) are their father and their uncle (see report of Case 1). The latter two patients' mother (S. S.) died at the age of 30. It is extremely likely that the affected members of both these families received their hereditary disposition ultimately from a common ancestor.

The material available is too scanty to allow definite conclusions concerning the mode of inheritance, but the positive findings support the contention that in the families in question the mode of inheritance was dominant, as it was in the large family studied by England and Denny-Brown.[1]

HISTOLOGICAL FINDINGS IN MUSCLES IN PROGRESSIVE NEUROPATHIC MUSCULAR ATROPHY

Since the observations were in principle similar in all cases, no complete description of the findings in the 20 biopsy specimens will be given. After the description of a particular case considered typical, the features of the muscular changes as revealed in the entire material will be presented in some detail. The

diagram in Figure 4, in which the findings in all biopsies are tabulated, makes clear the alterations in the individual cases and the variations observed and permits a comparison of the degrees of changes of various kinds. The cases are listed from left to right according to the duration of the disease in order to facilitate an evaluation of possible correlations between duration and histological changes.

CASE 1.—A. S., aged 36. *Duration of disease approximately one year.*

The pathological changes in the biopsy specimen taken from the gastrocnemius muscle were of moderate severity, and were well suited to illustrate the morbid alterations at their beginning. The primary muscle bundles could everywhere be easily identified, and the connective tissue separating them appeared not to be increased. However, in areas containing atrophic fibers there was a clear-cut increase of connective tissue, coarse and fine collagenous fibrils even lying between the individual atrophic muscle fibers.

The primary muscle bundles seen in cross sections were of three types: Some of them consisted exclusively of normal-sized fibers. The majority, however, contained normal-sized

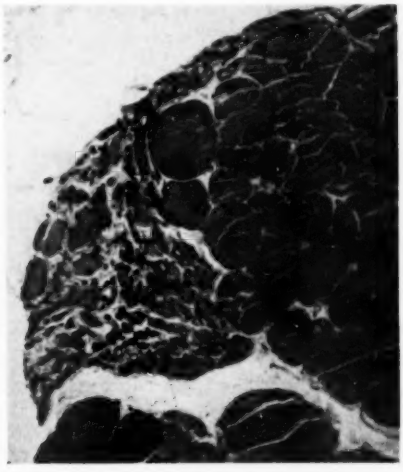


Fig. 3.—Photomicrograph (× 150) of section from the right gastrocnemius muscle in Case 1, at the age of 36, with duration of disease of approximately one year, showing grouping of atrophic fibers and moderate increase of connective tissue. Compare Figure 9.

fibers, a certain number of atrophic fibers, and a smaller contingent of hypertrophic fibers. The third type was represented by a few bundles, which were made up chiefly of atrophic fibers, a few normal-sized fibers, and scattered hypertrophic fibers.

The diameters of the majority of the atrophic fibers varied from 4 to 24 μ, while others had a diameter of about 35 μ. The atrophic fibers were characteristically collected into groups of from 10 or 12 to 80. These were frequently found in the peripheral part of a primary muscle bundle, either as a band along its surface or as a more compact group in a "corner" of the bundle (Figs. 3 and 9). Less frequently, strands of atrophic fibers extended into the interior of the bundle, intermingling with fibers the majority of which were normal. The diameters of the atrophic fibers in these groups were usually about 10 μ. Fibers of 30 μ diameter or a little more were far less frequent, but also these were as a rule clumped together.

The hypertrophic fibers usually had a diameter of about 100 μ, the largest fiber observed being 130 μ. These fibers, although occasionally occurring in groups of three to six, presented no clear-cut aggregation into larger groups but were chiefly seen in bundles containing atrophic fibers.

The number of muscle fiber nuclei was slightly increased. Occasionally a centrally placed nucleus was seen, but most of the nuclei were hypolemmal. In longitudinal sections of atrophic fibers these nuclei could be seen arranged in clumps or rows of 5 to 10. The nuclei in normal or hypertrophic muscle fibers appeared to be normal. In the atrophic fibers, however, the majority of the nuclei were hyperchromatic and usually smaller than normal. They varied somewhat in shape, particularly the smallest ones, which were compact and pyknotic. Now and then a picture of what appeared to be karyolysis or karyorrhexis could be seen, but normal nuclei also occurred in the atrophic fibers. Some of the nuclei in atrophic fibers were surrounded by a zone of lightly stained sarcoplasm, appearing as a halo or a lacuna around a usually pyknotic nucleus.

Signs of sarcoplasmic degeneration were not conspicuous and were observed only in clearly atrophic fibers. Cleavage or splitting of muscle fibers was not present. The cross striations, as seen in longitudinal sections, might be remarkably well preserved in atrophic fibers, even in fibers having a diameter of only 4 μ. Other fibers of 4 μ or more had sometimes lost their cross striations. In some fibers cut longitudinally a peculiar picture was seen, one part of the fiber having preserved its cross striations, the other having lost them.

Annulets were not observed. In a muscle spindle seen in cross section only one of the intrafusal muscle fibers was clearly defined, the others fusing to an indefinite mass.

A nerve bundle cut longitudinally and another cut transversely, as well as some small vessels, showed no clear-cut abnormalities. There appeared to be an abundance of capillaries in the atrophic areas of the muscle.

GENERAL HISTOLOGICAL FEATURES

The histological changes described in Case 1 appear to be typical of those encountered in the early stages of progressive neuropathic muscular atrophy of the Charcot-Marie-Tooth type, or in muscles recently affected. In more advanced stages some of the alterations described are more conspicuous; others less so. The various histological features will be considered separately in the order in which they are listed in Figure 4.

In the comparison of histological changes in biopsy specimens from different patients, it would have been desirable that the specimens in all cases be taken from the same muscle, and that they be taken from parts of the muscle presenting clinically similar degrees of atrophy. Except in Case 1, in which the biopsy specimen was from the gastrocnemius muscle, one biopsy specimen was always taken from the anterior tibialis muscle. In three of the cases another biopsy specimen was taken from a clearly affected muscle (Fig. 4), and in two cases (8 and 12) supplementary biopsy material from muscles clinically not affected was available. The muscle material chosen for biopsy, therefore, appears to be sufficiently similar to permit comparison. With regard to the stage of the pathological process in the piece of muscle removed, care was taken to select a piece at the clinically visible transition between normal and affected muscle. Despite this, some of the histological variations observed may conceivably have been due to differences in the site chosen for taking the biopsy specimen. This factor of uncertainty must be borne in mind when the degrees of changes in different cases are compared.

In Figure 4, an open circle denotes normal findings. When changes were present, an attempt was made to indicate them quantitatively by filling in in black a smaller or a greater sector of the circle. A total black circle, thus, represents the maximum of pathological changes of the particular kind; for example, in the case of the degree of atrophy it indicates that all muscle fibers present were atrophic. The commonest diameters of the atrophic fibers are listed in microns. In Case 2, for example, the figures *8-16* and *30-40* mean that the atrophic fibers were of two types with

regard to diameters, those of diameters ranging roughly from 8 to 16 μ, and those of diameters ranging from 30 and 40 μ, respectively. Similarly, the figures given for hypertrophic fibers indicate their commonest and maximal diameters. The degree of hypertrophy is checked against the presence of normal-sized fibers. A circle half-black and half-white, therefore, means that of the nonatrophic fibers, 50% are normal and 50% hypertrophic.

While it is possible to make fairly exact quantitative estimations with regard to the numbers of atrophic, normal, and hypertrophic muscle fibers, this is practically impossible with regard to the other changes studied. For these features, therefore,

Case	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Duration of disease in years	1	2	2	3	4	4	8	9	12	22	23	29	37	?
Age at examination	36	3½	43	40	31	42	53	27	47	29	55	58	59	64
Muscle examined	gast. crem. dext.	tib. ant. sin.	tib. ant. dext.	tib. ant. sin.	tib. ant. sin.	tib. ant. sin.	tib. ant. dext. / gast. crem. dext.	tib. ant. sin. / vast. lat. sin.	tib. ant. sin.	tib. ant. dext.	tib. ant. sin. / ant. dext.	tib. ant. sin. / brach. rad. sin. / rect. fem. dext.	tib. ant. sin. / vast. lat. sin.	tib. ant. sin.
Increase of connect. tissue	◔	◐	◐	◔	◕	◕	◕	◕	◐	●	◕ / ◐	◕ / ○ / ○	● / ◕	◔
Increase of adipose tissue	◔	◕	◕	○	○	◔	◐	◕ / ○	◔	◐	● / ◕	◕ / ○ / ○	◕ / ◕	○
Atrophy of muscle fibers (diameters in μ)	20-40 6-18	30-40 8-16	30-40 6-20	35-45 8-28	8-28	30-40 12-28	35-40 8-12 / 35-45 10-28	30-40 8-12	25-40 4-28	ca. 40 8-28	35-45 8-28 / 12-28	8-12	30-40 8-12 / grad. trans. to 8-12	10-28
Hypertrophy (diameters in μ)	90-130	90-150 100	80-100 190	100-120 190	100-110 160	90-110 170	90-110 150	90-110 180	90-110 180	60-100	80-130 160 / 90-120 200	90-110 200 / ca. 100 / ca. 100	90-110 180	90-110 160
Grouping of atrophic fibers	●	●	◕	◕	◕	◐	◕	◐	◐	◔	◐ / ◐	◔ / ◔ / ○	◔ / ◕	◕
Central nuclei	○	○	◕	◔	○	◕	◕	◐	◕	◕	◐ / ◐	◔ / ◔ / ◔	◕ / ◔	◔
Increase of hypolemmal nuclei	◔	◕	◕	◕	◕	◐	◕	◐	◐	◕	◕ / ◐	◐ / ◔ / ◔	◐ / ◐	◕
„Sick" nuclei	◔	◕	◐	◕	◕	◐	◐	◐	◐	◕	◕ / ◐	◐ / ◔ / ◔	◕ / ◐	◔
Pycnotic nuclei	◔	◔	◐	◔	◕	◐	◐	◐	◕	◕	◕ / ◐	◐ / ○ / ○	◕ / ◐	○
Nuclei with halo	◔	◔	◕	◔	◔	◐	◕	◕	◔	◔	◕ / ◕	◔ / ○ / ○	◕ / ◕	○
Sarcoplasmatic degeneration	◔	◔	◐	◕	◔	◐	◐	◐	◕	◐	◐ / ◕	◐ / ○ / ○	◕ / ◐	○
Cleavage	○	◔	◕	◕	◕	◐	◕	◐	◐	◐	◕ / ◕	◔ / ◔ / ◕	◔ / ◕	◕
Loss of cross striation	◔	◔	◐	◕	◔	◕	◕	◕	◕	◐	◐ / ◕	◕ / ○ / ○	◐ / ◕	○

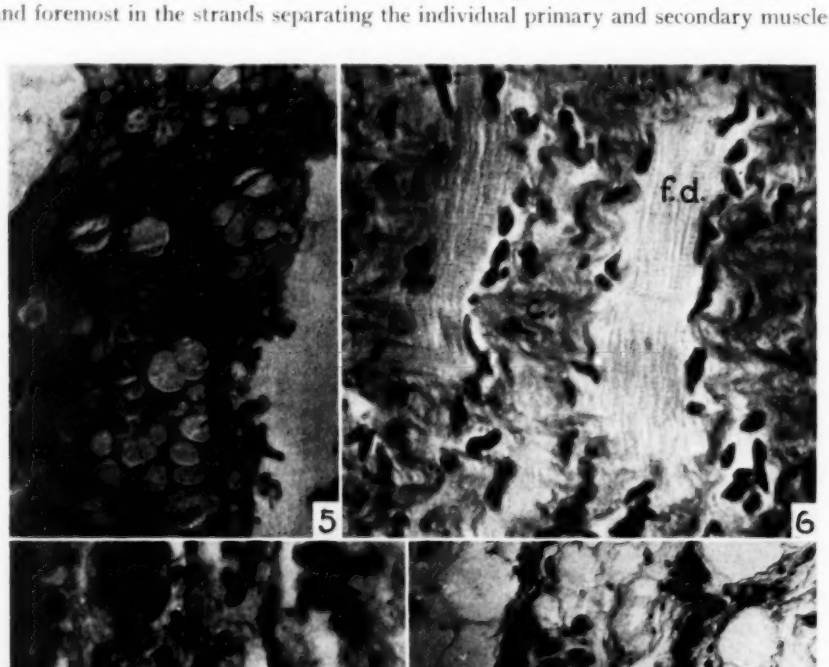
Fig. 4.—Diagrammatic representation of all biopsy findings. The degree of changes of various kinds are indicated approximately by the size of the black sector of the circles. Further explanation is given in the text.

the indications given in Figure 4 are only relative. Thus, a circle half-white, half-black, in the column "pycnotic nuclei" does not mean that half of all muscular nuclei were pyknotic, but merely serves to indicate a medium degree of nuclear changes of this type observed in the material. In spite of the subjective factor inherent in such judgments, we feel that their inclusion in the diagram is justified, since they give some idea of the intensity of the various changes observed in the individual cases.

While the incidence of the chief findings can thus be seen in Figure 4, some comment is appropriate for the elucidation of special points.

Increase of Connective Tissue.—This was a regular feature in all cases. As is seen in Figure 4, it was most marked in cases of long-standing disease, and on the whole was more pronounced the more advanced the atrophy of the muscle. Increase of connective tissue and atrophy of muscle fibers appeared to progress apparently at a proportional rate.

Connective tissue was increased chiefly in clearly atrophic areas of the muscle, and as a rule it was composed of rather coarse collagenous fibrils. It was seen first and foremost in the strands separating the individual primary and secondary muscle



Figs. 5-8.—*5* (Case 10), heavy increase of connective tissue, with collagenous fibrils extending between individual muscle fibers of the primary bundles, in a late stage of the disease. × 48.

6 (Case 3), rather dense connective tissue (*c.*) between fragments of atrophic muscle fibers with preserved cross striations and slight fibrillary disruption (*f. d.*). × 430.

7 (from same section as *6*), loose connective tissue (*c.*), with sparse and relatively fine collagenous fibrils, between muscle fibers showing sarcoplasmic degeneration (*s. d.*). × 430.

8 (Case 11), adipose tissue between small groups of severly atrophic muscle fibers in left anterior tibialis muscle in a case of advanced muscular atrophy and long duration of the disease. See Figure 1*A*. × 150.

bundles. With more advanced degrees of atrophy, there was, as a rule, a clear-cut increase in connective tissue also within the primary bundles, collagenous fibrils encircling individual muscle fibers (Fig. 5). Where the atrophic fibers had preserved their structure, the connective tissue was as a rule rather dense (Fig. 6), but where the atrophic muscle fibers presented signs of degeneration and disintegration the

connective tissue was on the whole more loosely structured, composed of thinner collagenous fibrils, and less abundant (Fig. 7). In advanced stages, increase of connective tissue was seen not only between atrophic fibers but also between normal and hypertrophic fibers.

Increase of Adipose Tissue.—This was seen to some extent in almost all cases, and, like the increase in connective tissue, was more pronounced the longer the duration of the disease and the more advanced the muscular atrophy. However, the increase in adipose tissue was not as marked as the proliferation of connective tissue, although it appeared to follow this. Thus, it appeared to begin between the bundles, and only in very advanced stages of atrophy might fat cells be seen between the remaining atrophic muscle fibers (Fig. 8), and even between normal and hypertrophic fibers.

Degree of Muscular Atrophy.—This feature is represented quantitatively in Figure 4. As is well known, fibers in normal muscle vary somewhat with regard to their diameter, not only at different ages but even within the same muscle or primary muscle bundle. In the present study muscle fibers having in adult persons diameters between 50 and 80μ have been considered normal. This is in agreement with the data given by Häggqvist,[8] who cited Halban's [9] value of an average fiber diameter of 62.5μ for the gastrocnemius and anterior tibialis muscles and Hauck's [10] value of 61.3μ. Von Meyenburg [11] regarded fibers exceeding 70 to 80μ in diameter as hypertrophic. Consequently, fibers having a diameter of less than 50μ have been considered atrophic in the present study.

Atrophy of muscle fibers was present in all biopsy specimens from clinically affected muscles (Figs. 4 and 9). However, there were wide variations with regard to the number of atrophic muscle fibers, as well as to the degree of atrophy of the fibers. As will be seen in Figure 4, the percentage of atrophic fibers present in the biopsy tissue showed a clear-cut increase roughly proportional to the duration of the disease. Furthermore, in those cases in which a biopsy specimen was taken from an anterior tibialis muscle and from another, clinically less affected, muscle (e. g., Case 11, left and right anterior tibialis muscles; Fig. 1*A*), the degree of atrophy was less in the clinically less affected muscle.

With regard to the degree of atrophy of individual muscle fibers, it is striking to observe how the atrophic fibers may apparently be of two types (Fig. 9). Some fibers had a diameter of about 35μ and were thus moderately atrophic. Other atrophic fibers had diameters averaging about 10μ, with a range of 4 to 25 μ. A clear-cut example of this difference is found in Case 2 (Fig. 10), in which even whole primary bundles were composed of normal fibers throughout (*n.*, Fig. 10),

8. Häggqvist, G.: Gewebe und Systeme der Muskulatur, in von Möllendorff, W., Editor: Handbuch der mikroskopischen Anatomie des Menschen, Vol. 2, Pt. 3, Berlin, Springer-Verlag, 1931, pp. 105-237.

9. Halban, J.: Die Dicke der quergestreiften Muskelfasern und ihre Bedeutung, Anat. Hefte **3**:267-308, 1893.

10. Hauck, L.: Untersuchungen zur normalen und pathologischen Histologie der quergestreiften Muskulatur, Deutsche Ztschr. Nervenh. **17**:57-70, 1900.

11. von Meyenburg, H.: Die quergestreifte Muskulatur, in Henke, F., and Lubarsch, O., Editors: Handbuch der speziellen pathologischen Anatomie und Histologie, Vol. 9, Pt. 1, Berlin, Springer-Verlag, 1929, pp. 299-507.

of slightly atrophic fibers, of about 30μ (*m.*, Fig. 10), or of severely atrophic fibers only, having a diameter of 8 to 16μ (*s.*, Fig. 10). However, in all cases, fibers in transitional degrees of atrophy occurred in a certain number of bundles.

Grouping of Atrophic Muscle Fibers.—In biopsy specimens from clinically affected muscles the atrophic muscle fibers were as a rule clearly grouped. From 10 to 80 fibers in the same stage of atrophy were aggregated in a "corner" of a primary bundle, lay along its periphery, or extended as strands into the interior of the bundle (Figs. 3 and 10 and the drawings of Figure 9, representing samples from all 14 cases). The drawings make clear that the grouping is most pronounced in a disease of short duration, of a few years. Almost all atrophic fibers may then be aggregated into groups, but even after a duration of 37 years (Case 13) groups of 10 to 20 muscle fibers in the same degree of atrophy can be found, although at late stages the atrophic fibers tend to predominate, intermingled with normal or hypertrophic fibers (Fig. 9). When slightly atrophic, as well as severely atrophic, fibers were present in the same biopsy specimen, each group of atrophic fibers usually consisted of fibers of one type only, but groups of both types might be present in the same primary bundle. At the border of such atrophic fiber groups, there was usually some intermingling with normal or hypertrophic fibers.

Hypertrophic Muscle Fibers.—As previously mentioned, fibers exceeding 80 μ in diameter were considered hypertrophic. Only in Case 2 was the upper limit chosen at 60μ, since the patient was only 3½ years old. Unlike the atrophic fibers, the relative number of hypertrophic fibers appeared to remain approximately constant, regardless of the duration of the disease. Frequently about one-half the remaining nonatrophic fibers were hypertrophic (Fig. 4). However, it appears that some time is required for the hypertrophy to develop, and it also seems that the hypertrophic fibers tend to disappear in later stages. Thus, in Case 13 not a single hypertrophic fiber was found in the biopsy specimen from the anterior tibialis muscle, while in the less affected quadriceps hypertrophic fibers were present. The commonest diameter of the hypertrophic fibers was 100 μ, but fibers of 180, and even 200μ, were seen (Fig. 4). The maximal values in the different cases are indicated in Figure 4. In cross sections the hypertrophic fibers had a circular, or more frequently an oval, outline, but occasionally it might be more irregular. The hypertrophic fibers frequently showed different alterations, to be described below.

Increase of Muscle Fiber Nuclei.—A distinction must be made between hypolemmal and centrally placed nuclei. A small number of centrally placed nuclei is normal.

Central nuclei occurred in increased numbers in biopsy material from all clinically affected muscles, except in cases in which the disease was of short duration (Fig. 4). In no case was the increase of central nuclei very marked, but it could be seen in atrophic, as well as in hypertrophic and normal, fibers.

Increase in hypolemmal nuclei was much more prominent. This was most evident in longitudinal sections, in which long rows of nuclei may be seen along the surface of the fiber (Figs. 11 and 16), but in transverse sections also this feature could frequently be seen, the nuclei forming an almost compact ring about the periphery of the fiber (Fig. 12). Increase of hypolemmal nuclei occurred chiefly in atrophic fibers, particularly in severely atrophic ones. The number of nuclei in such fibers by far exceeded that which could be considered a consequence of the

reduction in volume of the fiber. In normal and hypertrophic fibers some increase in the hypolemmal nuclei was also common. In general, there appeared to be a greater increase the more pronounced the atrophy of the fibers.

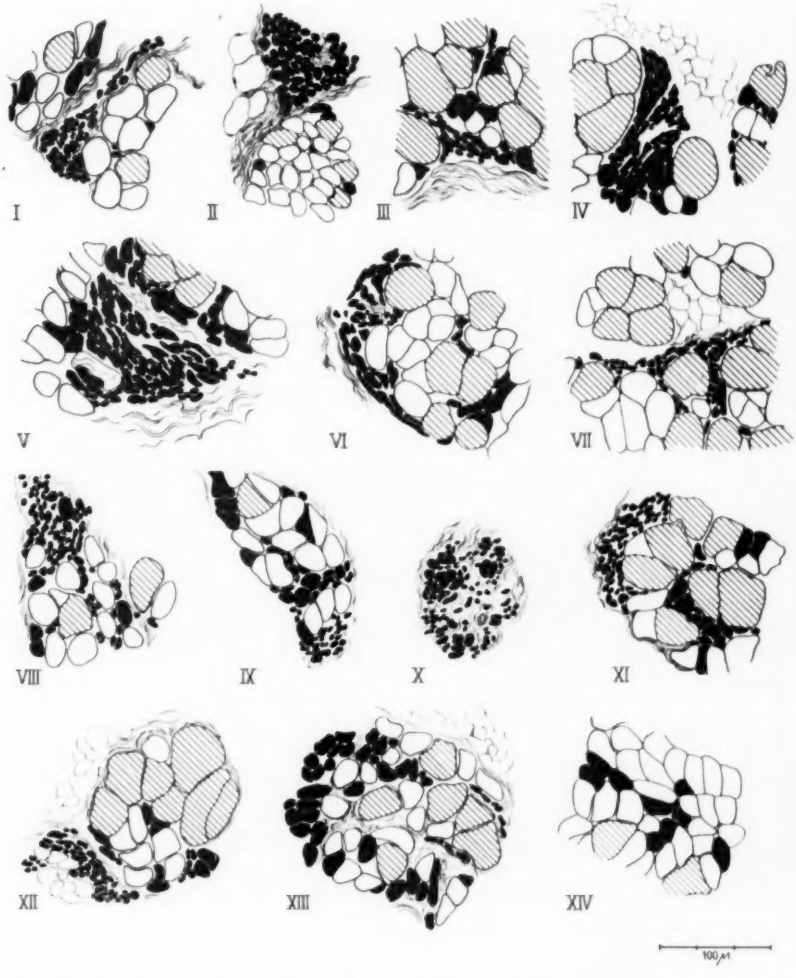
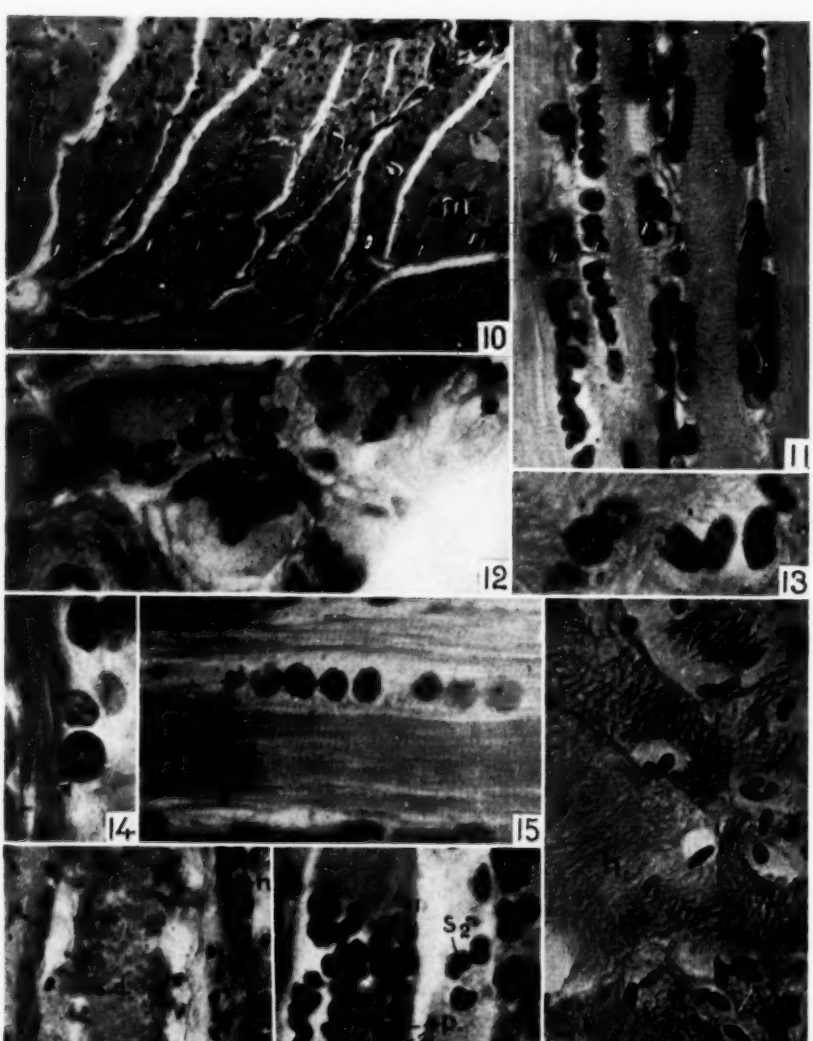


Fig. 9.—Drawings made by means of a projection apparatus of cross sections of muscle biopsy specimens in all 14 cases—in Case 1 from the gastrocnemius muscle; in Case 13, from the left vastus lateralis muscle; in all others, from the anterior tibialis muscle (Fig. 4). Normal-sized fibers are white; atrophic fibers, black; hypertrophic fibers, hatched. Note grouping of atrophic fibers and frequent occurrence of atrophic fibers of two sizes.

Nuclear Changes.—As is well known, the nuclei of normal muscle fibers vary considerably. According to Häggqvist,[8] Bowden and Gutmann,[12] and Gutmann

12. Bowden, R. E. M., and Gutmann, E.: Denervation and Reinnervation of Human Voluntary Muscle, Brain **67**:273-313, 1944.



Figs. 10-18.—*10* (Case *2*), grouping of atrophic fibers in anterior tibialis muscle (age 3½ years; duration of disease, two years). Some primary bundles (*s.*) are composed of severely atrophic fibers only (8 to 16 *μ*); others (*m.*), exclusively of fibers showing a medium degree of atrophy (about 30 *μ*); others, of normal fibers (*n.*). There is moderate increase of connective tissue. × 150.

11 (Case 11), increase of hypolemmal nuclei in atrophic muscle fibers. Most of the nuclei are not quite normal. × 530.

12 (Case 11), increase of hypolemmal nuclei in atrophic fibers, as seen in transverse section. In one of the fibers a dense aggregation of nuclei is seen extending to the center of the fiber. See also Figure 8. × 530.

13 (Case 5), "sick" nuclei in an atrophic muscle fiber, with coarse chromatin granules, chiefly, peripherally situated. × 970.

14 (Case 11), "sick" nucleus with a central vacuole in an atrophic muscle fiber. × 1,190.

15 (Case 7), rows of centrally placed "sick" nuclei in atrophic muscle fibers. × 530.

16 (Case 7), pyknotic nuclei (*p.*) arranged hypolemmally in rows in extremely atrophic fibers. A few normal nuclei (*n.*) are seen. Some of the fibers present sarcoplasmic degeneration (*s. d.*). × 150.

17 (Case 11), clumps of pathological nuclei in atrophic muscle fibers. Most of the nuclei are pyknotic (*p.*); others are "sick," having an unusually large nucleolus (s_1) or a very lightly stained karyoplasm (s_2). × 530.

18 (Case 6), nuclei with halo in atrophic and hypertrophic (*h.*) fibers with otherwise intact structure. Most of the nuclei are pyknotic. × 335.

and Young,[13] they form an elongated oval. The last authors gave their chief diameters as 4 X 12 μ in surface view. They contain one, two, or three large nucleoli. Some fibers have remarkably large, and others very small, nuclei. The nuclear membrane is usually distinct; the karyoplasm stains lightly and is finely granular or reticular. A small number of the nuclei are centrally placed, but most of them are hypolemmal. In the normal muscle fibers of the present material the nuclei appeared as described above. Occasionally a nucleus with three or four nucleoli was seen. When there were more nucleoli, one of them was commonly considerably larger than the others.

In all biopsy specimens of clinically affected muscles there were, in addition to the normal forms, nuclei presenting various changes which must be taken to betray pathological alterations. These abnormal nuclei were somewhat arbitrarily subdivided into three types: "sick" nuclei, pyknotic nuclei, and nuclei with a halo.

1. "Sick nuclei" are those showing slight changes. They were usually smaller than most of the normal nuclei and frequently had an irregular outline. The apparently least affected "sick" nuclei differed from the normal nuclei in having a more irregularly structured chromatin pattern or a very prominent nuclear membrane, or by the unusual size of one of the nucleoli (s_1 Fig. 17). In other nuclei, apparently more severely affected, nucleoli could not be clearly identified. Their karyoplasm might be either lightly stained and finely granular, or markedly hyperchromatic, consisting of coarse, irregular, dark-staining granules, frequently arranged along the nuclear periphery (Fig. 13). Sometimes vacuoles occurred in the "sick" nuclei of this type, particularly in the hyperchromatic nuclei (Fig. 14).

The nuclear changes described have been considered as signs of degeneration. Nuclei thus affected were seen chiefly, but not exclusively, in atrophic fibers. They were usually hypolemmal (Fig. 11), but sometimes they were centrally placed, and then frequently in long rows along the fiber (Fig. 15). The number of "sick" nuclei appeared to be relatively constant, regardless of the duration of the disease, at least when this was more than two years, but there was some indication that they increased in number according to the intensity of the disease, i. e., its rate of progression. No mitotic divisions were seen in these nuclei, but it was sometimes striking to observe how "sick" nuclei of one type could be found in rows or groups (Figs. 11 and 13). Although instances of an approximately equatorial narrowing of a nucleus might be seen, it is doubtful whether this could be interpreted as a sign of amitotic division. Pfitzner[14] and Forbus,[15] who also noted this feature, expressed a similar opinion.

2. The designation "Pyknotic" nuclei is used here for small nuclei, some 3 by 3 μ, usually round, and extremely hyperchromatic, so that no structure could be discerned in the karyoplasm and the nuclear membrane could not be distinguished. They were found in all biopsy material from clinically affected muscles, chiefly in atrophic fibers (Fig. 16). They were most commonly hypolemmal, but long rows of 5 to 20, or clumps of 5 to 50, pyknotic nuclei might also occur centrally in the atrophic muscle fibers (Fig. 17). Occasionally clumps of pyknotic nuclei were so

13. Gutmann, E., and Young, J. Z.: Reinnervation of Muscles After Various Periods of Atrophy, J. Anat. **78**:15-43, 1944.

14. Pfitzner, W.: Zur pathologischen Anatomie des Zellkerns, Arch. path. Anat. **103**:275-300, 1886.

15. Forbus, W. D.: Pathologic Changes in Voluntary Muscle, Arch. Path. **2**:318-339, 1926.

densely packed that the contours of the individual nuclei could not be made out (Fig. 17). The number of pyknotic nuclei had a tendency to increase with the duration of the disease, but the intensity of the process also appeared to be of importance.

3. Nuclei with a halo (Bowden and Gutmann[12]) were seen in all biopsy specimens from clinically affected muscles, but they were far less frequent than pyknotic nuclei. The halo might consist of partly disintegrated sarcoplasm, in which some structure was still visible, or it might be composed of a lightly stained, homogeneous substance, contrasting sharply with the surrounding sarcoplasm (Fig. 18), which might be normal or present signs of degeneration. Nuclei of these types occurred in muscle fibers of all types, but chiefly in less atrophic fibers. The nucleus itself might appear normal but as a rule was "sick," or pyknotic. Two or more such nuclei might occur together.

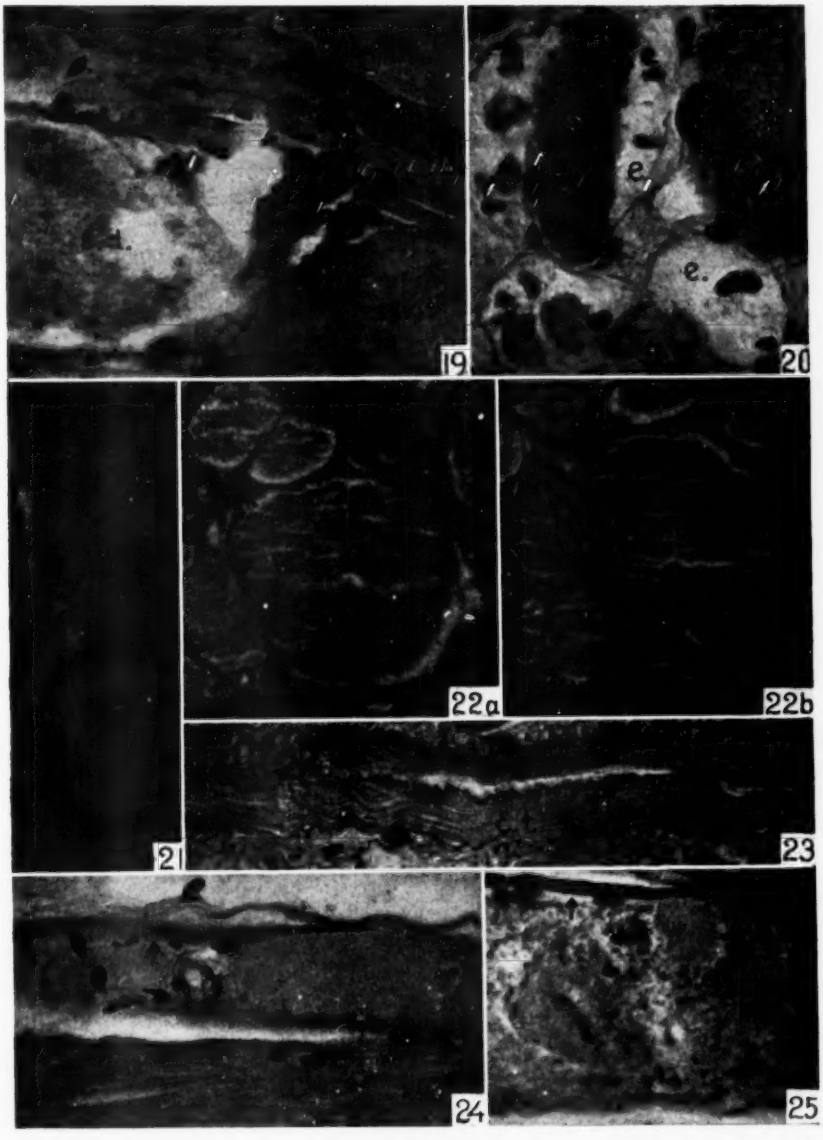
Sarcoplasmic Degeneration.—Signs of sarcoplasmic degeneration, such as granulation of sarcoplasm, "cloudy swelling," vacuolation, or fragmentation of sarcoplasm, increased with the duration of the disease but appeared to depend on the intensity of the pathological process. All types of fibers, atrophic, normal, and hypertrophic, might show evidence of sarcoplasmic degeneration (Fig. 19), but on the whole the change was most marked in atrophic fibers and in cases of long-standing disease. Sarcoplasmic degeneration might affect all or most of the fibers in a group, while an adjoining group of fibers might be severely atrophic but have preserved its cross striation (Fig. 19). In extreme stages there might be only remnants of degenerating sarcoplasm or some closely packed pyknotic nuclei, or the endomysial tubes might appear completely empty (Fig. 20). Similar pictures have been described by other authors in various conditions.[16] Hyaline degeneration was not seen in the material of this study.

Sarcoplasmic degeneration was usually accompanied with increase of nuclei, central as well as hypolemmal (Fig. 7). The nuclei then as a rule were "sick" or pyknotic, but they might appear normal, and degeneration was sometimes present without nuclear increase (Figs. 16 and 19), particularly in nonatrophic fibers. Very commonly only part of a muscle fiber presented sarcoplasmic degeneration. Of particular interest is the observation that atrophic fibers which had cross striations intact at a certain place might increase rather abruptly in diameter and show distinct sarcoplasmic degeneration (Fig. 21).

Cleavage.—This term is used here in the sense indicated by Wohlfart;[17] i. e., cleavage is characterized by the longitudinal ingrowth into a muscle fiber of a septum of connective tissue, containing nuclei and frequently capillaries. Cleavage

16. (*a*) Bowden and Gutmann.[12] (*b*) Forbus.[15] (*c*) Waldeyer, W.: Über die Veränderungen der quergestreiften Muskeln bei der Entzündung und dem Typhusprozess, sowie über die Regeneration derselben nach Substanzdefecten, Arch. Path. Anat. **34**:473-514, 1865. (*d*) Strümpell, A.: Zur Lehre von der progressiven Muskelatrophie, Deutsche Ztschr. Nervenh. **3**:471-501, 1893. (*e*) Hassin, G. B., and Dublin, W.: Histopathology of Muscles in the Spinal Type of Progressive Muscular Atrophy, J. Neuropath. & Exper. Neurol. **4**:240-249, 1945. (*f*) Bowden, R. E. M., and Gutmann, E.: Observations in a Case of Muscular Dystrophy, with Reference to Diagnostic Significance, Arch. Neurol. & Psychiat. **56**:1-19, 1946. (*g*) Clark, W. E. Le Gros: An Experimental Study of the Regeneration of Mammalian Striped Muscle, J. Anat. **80**: 24-36, 1946.

17. Wohlfart, G.: Dystrophia Myotonica and Myotonia Congenita: Histopathologic Studies with Special Reference to Changes in the Muscles, J. Neuropath. & Exper. Neurol. **10**:109-124, 1951.



Figs. 19-25.—*19* (Case 7), severely atrophic fibers, 4 to 12 μ, with preserved cross striations and pyknotic nuclei, and hypertrophic fibers presenting sarcoplasmic degeneration (*s. d.*) without nuclear increase. Below to the right is a normal fiber (*n.*). × 335.

20 (Case 7), cross section of muscle fibers showing different degrees of sarcoplasmic degeneration. In some the endomysial tubes are more or less empty (*e.*). × 750.

21 (Case 7), atrophic muscle fiber having preserved cross striations in its extremely atrophic part (*a.*) but degenerated sarcoplasm (*s. d.*) in its thicker part. × 750.

22 a and *b* (Case 10), hypertrophic muscle fiber (90 by 100 μ) showing cleavage. The photomicrograph in *b* is taken several sections removed from that in *a* and shows a thin connective tissue septum (arrow) subdividing the thick fiber in *a* into two parts. × 390.

23 (Case 12), longitudinal section of a muscle fiber showing splitting. Note the connective tissue strand (*c. t.*) in the space between fiber segments. × 335.

24 (Case 7), atrophic muscle fiber with preserved myofibrils in its peripheral zones (arrows) and central area of sarcoplasmic degeneration. × 335.

25 (Case 11), extremely atrophic muscle fiber (2-μ diameter), with preserved cross striations (arrow) adjoining 70-μ fiber with sarcoplasmic degeneration. × 530.

was seen in all biopsy material from clinically affected muscles, except in Case 1. Most of the fibers showing cleavage were moderately atrophic or hypertrophic (Fig. 22), an observation probably explaining why little cleavage was seen in Case 13, in which most of the fibers were severely atrophic.

Several fibers presenting cleavage were followed in serial transverse sections in Cases 5, 8, 10, and 13. The segments of a muscle fiber produced by ingrowth of connective tissue might sometimes taper off and be replaced by connective tissue, as shown in Figure 26 (fibers a_1 and a_2), or two separated segments (b_2 and b_3, Fig. 26) might again join each other. Occasionally segments of a fiber were seen to retain their size for a considerable distance, and the strand might also produce a certain diastasis, indicating a real splitting of the fiber (Fig. 23). In longitudinal

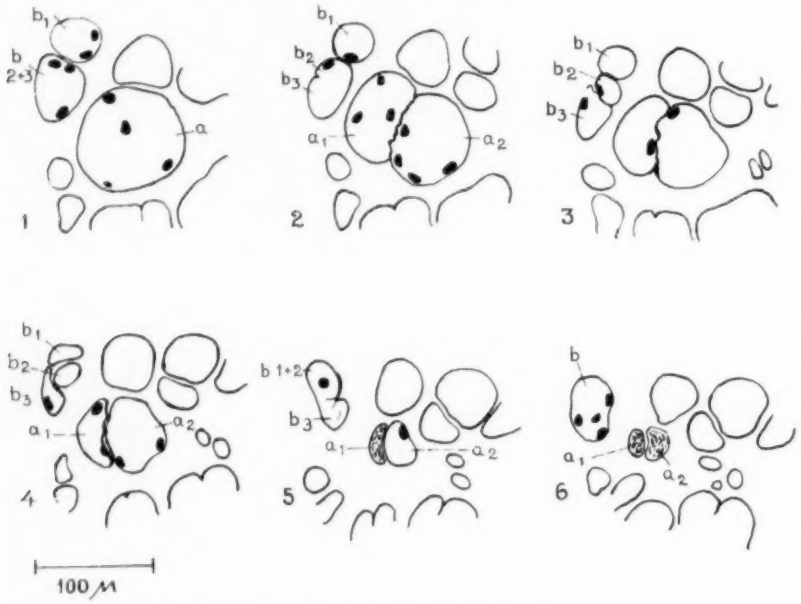


Fig. 26.—Drawings made by means of a projection apparatus of transverse serial sections from the anterior tibialis muscle in Case 10, demonstrating cleavage of muscle fibers. A few sections are omitted between each of those drawn.

sections, a capillary loop in the middle of a muscle fiber was sometimes seen. Similar pictures were described by Wohlfart [17] and Lewin.[18]

Loss of Cross Striation.—This alteration was seen particularly in fibers with moderate or severe atrophy and was found in all biopsy specimens from clinically affected muscles. The disappearance of cross striations might affect the entire width of the fiber, or be confined to part of it, for example, its central zone (Fig. 24). In fibers showing sarcoplasmic degeneration patches with preserved cross striations might occur. Several such fibers were studied also by polarized light, but no cross striations were seen in the degenerated areas, contrary to the reports of Bowden and Gutmann.[12]

18. Lewin, A.: Zur Pathologie der progressiven Muskelatrophie und verwandter Zustände, Deutsche Ztschr. Nervenh. **2**:139-176, 1892.

While loss of cross striations was common where there was sarcoplasmic degeneration, cross striations might be well preserved where the fiber was fragmented or vacuolated or where the myofibrils were separated (fibrillary disruption, Fig. 6). In all biopsy specimens showing extremely atrophic fibers cross striations were preserved throughout the length of many such fibers included in the section, even if the fiber diameter was only 3 to 4 μ, or even not more than 2 μ (Fig. 25). In such severely atrophic fibers with preserved cross striations the nuclear increase was purely hypolemmal, but when the cross striation was lost, the nuclear increase was as a rule both hypolemmal and central.

Annulets.—Such structures, common in dystrophia myotonica,[17] were not observed in the present material.

Nerves and Blood Vessels.—Some of the arteries seen in the preparations appeared to have somewhat thickened walls but otherwise showed no definite changes. Smaller nerve trunks also appeared normal. Convincing pictures of nerves containing normal, as well as empty, endomysial tubes were not seen, but the staining methods employed were not favorable for a study of these features.

Muscle Spindles.—In six cases muscle spindles were included in the biopsy specimens. In Cases 1 and 3 the intrafusal fibers did not appear quite normal, and in Case 3 the connective tissue capsule of the spindle was thickened.

COMMENT

For reasons given in a preceding section, we feel certain that the clinical diagnosis of progressive neuropathic muscular atrophy is justified in all cases included in the present study. Some points of clinical interest are touched upon. The following comments are limited to the histological findings and to correlations of these with the clinical aspects of the disease.

When the findings in this study are compared with those made in studies of other types of muscular atrophy, the earlier stages of the disease process should chiefly be considered, since at later stages the differences tend to disappear.

As most recently and most fully documented by Wohlfart,[2d] the occurrence of groups of muscle fibers in the same stage of atrophy is a typical feature in muscular atrophies due to damage to peripheral motor neurons. The pictures of cross sections of muscles in such diseases given by Wohlfart,[2d] as well as those published by Slauck,[2a,b] Wohlfahrt and Wolfart,[2c] Karlstrøm and Wohlfart,[19] Bang and others,[20] Hipps,[21] Brandt,[22] and others are essentially similar to those reproduced

19. Karlstrøm, F., and Wohlfart, G.: Klinische und histopathologische Studien über infantile spinale Muskelatrophie (Oppenheimsche und Werdnig-Hoffmannsche Krankheit), Acta psychiat. et neurol. **14**:453-488, 1939.

20. Bang, J.; Einarson, L.; Fog, M., and Ringsted, A.: Treatment of Some Neuromuscular Diseases with Synthetic Vitamin E (Amyotrophic Lateral Sclerosis and Progressive Muscular Dystrophy), Nord. med. **10**:1201-1212, 1941.

21. Hipps, H. E.: Clinical Significance of Certain Microscopic Changes in Muscles of Anterior Poliomyelitis, J. Bone & Joint Surg. **24**:68-80, 1942.

22. Brandt, S.: Werdnig-Hoffmann's Infantile Progressive Muscular Atrophy: Clinical Aspects, Pathology, Heredity and Relation to Oppenheim's Amyotonia Congenita and Other Morbid Conditions with Laxity of Joints or Muscles in Infants, translated from Danish by H. Anderson, Copenhagen, Ejnar Munksgaards, Forlag, 1950; Course and Symptoms of Progressive Infantile Muscular Atrophy: Follow-Up Study of 112 Cases in Denmark, Arch. Neurol. & Psychiat. **63**:218-228, 1950.

in Figure 9 of the present study. Furthermore, the increase predominantly in hypolemmal nuclei in early stages of progressive neuropathic muscular atrophy of the Charcot-Marie-Tooth type is in agreement with the findings in atrophies of neural origin, as is the relatively moderate increase of connective tissue and the even slighter increase of adipose tissue. The similarities of the histological changes in our cases to those observed in different types of muscular atrophies due to disease of peripheral motor neurons strongly support the belief that the muscular changes in the Charcot-Marie-Tooth type of progressive neuropathic muscular atrophy are to be attributed to a primary disturbance of the nervous system.

The same conclusion was reached previously by Brodal and Refsum [3] on the basis of the findings in Case 8 of the present material, and Wohlfart [24] described briefly another confirmatory case. Cassirer and Maas,[23] Bowden and Gutman,[16f] and Welander [24] also found muscular changes of the same kind in one, one, and eight cases, respectively. Further support for the concept comes from electromyographic studies. Buchthal and Clemmesen [25] and Kugelberg [26] showed that the electromyographic patterns in progressive muscular atrophies of spinal origin differ from those in muscular dystrophies in certain respects and that in atrophy of the Charcot-Marie-Tooth type the electromyographic findings are similar to those in the former group. In cases of the present study in which electromyographic investigations were undertaken, the findings were in agreement with those of the authors cited. It is of interest, also, that the test for ribose in the urine, recently devised by Orr and Minot [27] and found to be positive in cases of progressive dystrophies and negative in cases of progressive muscular atrophies of spinal origin, was found by these authors to give negative results in the Charcot-Marie-Tooth type.

Histological and electromyographic studies thus indicate that the muscular atrophy in the disease under consideration is due to a morbid process affecting the peripheral motor neurons. Studies of this kind, however, do not give any information as to which part of the neuron, its axon or its perikaryon, is primarily affected, or as to other possible sites of the disease in the nervous system. Several authors, cited by England and Denny-Brown,[1] have described, in addition to lesions of peripheral motor neurons, pathological changes in the dorsal roots and the dorsal funiculi of the cord which explain the sensory changes observed. In view of these findings, one might expect to see pathological changes in the sensory organs of the muscle, of which the muscle spindles are best suited to examination in biopsy material. However, our studies have not given convincing results with respect to this point.

23. Cassirer, and Maas, O.: Beitrag zur pathologischen Anatomie der progressiven neurotischen Muskelatrophie, Deutsche Ztschr. Nervenh. **39**:324-340, 1910.

24. Welander, L.: Myopathia distalis tarda hereditaria, Acta med. scandinav. Supp. **265**: pp. 1-124, 1951.

25. Buchthal, F., and Clemmesen, S.: On the Differentiation of Muscle Atrophy by Electromyography, Acta psychiat. et neurol. **16**:143-181, 1941; The Electromyogram of Atrophic Muscles in Cases of Intramedullar Affections, ibid. **18**:377-388, 1943.

26. Kugelberg, E.: Electromyograms in Muscular Disorders, J. Neurol., Neurosurg. & Psychiat. **10**:122-133, 1947; Electromyography in Muscular Dystrophies: Differentiation Between Dystrophies and Chronic Lower Motor Neurone Lesions, ibid. **12**:129-136, 1949.

27. Orr, W. F., and Minot, A. S.: Ribosuria: A Clinical Test for Muscular Dystrophy, A. M. A. Arch. Neurol. & Psychiat. **67**:483-486, 1952.

The regular occurrence of muscle fibers in the same stage of atrophy in more or less well-circumscribed groups has been interpreted as reflecting the distribution of fibers belonging to one or a few motor units (Wohlfart [20]). This seems to be a reasonable explanation of the most characteristic feature in the histological picture in cases of amyotrophic lateral sclerosis, progressive spinal muscular atrophy, syringomyelia [28] and infantile progressive muscular atrophy.[29] In denervation atrophy [12] and poliomyelitis [21] similar findings have been made. It is in agreement with recent experimental studies [30] that the different groups are not sharply delimited in cross sections but that fibers of one group intermingle to some extent with those of neighboring ones. This, of course, can be seen only when the fibers of different groups are affected with different degrees of atrophy. It is clearly evident in many of our cases.

If the muscular atrophy in Charcot-Marie-Tooth disease is due to a primary disease of the peripheral motor neurons, one might expect the muscle fibers to be affected by what is commonly called "simple atrophy," characterized chiefly by steadily progressing diminution in size and pyknotic nuclei, without other pronounced changes. Some increase in connective tissue would appear likely, as would also an apparent increase in the number of the hypolemmal nuclei. However, as has been seen, in all biopsies of the present study muscle fibers and their nuclei presented changes which would be designated as degenerative. The question might therefore be raised whether, in addition to the disease of peripheral motor neurons, other pathogenic factors are responsible for the muscular changes.

A study of the pertinent literature, as well as personal observations, makes clear that degenerative changes of the same kind as those seen in the present material are met with in other types of progressive muscular atrophy attributed to lesions of peripheral motor neurons, but they are less pronounced than in most cases of this investigation.[16e] Studies of muscles in peripheral nerve injuries in man are valuable for comparison. Bowden and Gutmann [12] described various types of nuclear degeneration, including pyknotic nuclei and nuclei with haloes, increase in central nuclei, sarcoplasmic degeneration, and fibrillary disruption. However, except for an increase in the number of nucleoli, which appears during the first three months, these features become marked only when the denervation has lasted more than three years. Similar "degenerative" changes have been described in experimental denervation studies.[31] They appear, however, to develop more rapidly in the cat than in man and to be exceptional in the opossum.[32] The occurrence of "degenerative" changes in the atrophic muscle fibers, thus, does not contradict the assumption that the muscular changes are due entirely to primary disorder of the peripheral motor neurons even if no adequate explanation of their occurrence can be given at present. The fact that such changes are more pronounced in pro-

28. Wohlfahrt and Wohlfart.[2e] Wohlfart.[20] Bang and others.[29]

29. Karlström and Wohlfart.[19] Brandt.[22]

30. Feindel, W.; Hinshaw, J. R., and Weddell, G.: Pattern of Motor Innervation in Mammalian Striated Muscle, J. Anat. **86**:35-48, 1952. van Harreveld, A.: Structure of the Motor Units in the Rabbit's M. Sartorius, Arch. néerl. physiol. **28**:408-412, 1947.

31. Tower, S. S.: Atrophy and Degeneration in Skeletal Muscle, Am. J. Anat. **56**:1-43, 1935.

32. Sunderland, S., and Ray, L. J.: Denervation Changes in Mammalian Striated Muscle, J. Neurol., Neurosurg. & Psychiat. **13**:159-177, 1950.

gressive muscular atrophy of the Charcot-Marie-Tooth type than, for example, in amyotrophic lateral sclerosis or infantile progressive muscular atrophy may reasonably be explained by the different durations of the diseases. Only in the slowly progressive Charcot-Marie-Tooth atrophy will there be time for the "degenerative" changes to develop to a conspicuous degree. This conclusion is supported by the findings in the present study, since "degenerative" changes were rather moderate in patients who had their disease for four years or less and in general showed a tendency to increase the longer the process had lasted.[33] It appears permissible, thus, to consider the "degenerative" changes as representing late stages in the atrophic process, and there seems to be no need to invoke factors other than a disorder of the peripheral motor neurons to explain the muscular changes, except for possible secondary consequences of the denervation, such as impaired circulation. Tower's [31] systematic experimental studies lend weighty support to this view.

From a survey of the material of the present study, it is possible to reconstruct the development of muscular changes fairly well. The first alterations consist of an atrophy in groups of muscle fibers belonging to the damaged motor neurons, and in early stages this is the most distinctive finding (Cases 1 to 5; Fig. 4). Concomitantly, there is an increase of the connective tissue between the primary bundles and, to some extent, also of the collagenous fibrils surrounding the individual atrophic fibers. The atrophy sometimes seems to reach a marked degree rather rapidly, fibers of less than 10μ being very common. The simultaneous presence of much less affected fibers may be due to their motor neurons having been affected later. However, it is striking (and the same feature is seen in amyotrophic lateral sclerosis) that in almost all cases the atrophic fibers may be of two types. They are either very small, 2 to 20μ in diameter, or only moderately atrophic, 30 to 40μ. Fibers with diameters of 20 to 30μ are rather infrequent. This finding seems to indicate that the atrophy takes place in two stages, the affected fibers first attaining a moderate degree of atrophy and the process then rather abruptly passing to the more extreme degrees; other explanations, however may be suggested.

As the atrophy proceeds, the numerical increase in atrophic fibers and the continued proliferation of connective tissue to some extent obscure the pattern of grouping. With more advanced atrophy there is a tendency to some increase of adipose tissue. As shown in Figure 4, Case 13 is an exception, the muscle tissue in this case presenting almost maximal fibrosis but only a moderate increase of adipose tissue. The patient had been very active in exercising in order to maintain what was left of muscular power in his legs (walking and bicycling, although with some difficulty). This may explain the scanty infiltration of fat in his muscles, in agreement with Hipps's [21] finding of corresponding variations in fat in trained and inactive paretic muscles in poliomyelitis.

33. A strict correspondence between the degree of histological change and the duration of the disease, can, of course, not be expected. In addition to the uncertainty inherent in selecting muscles affected to the same degree clinically, the patient's information as to the time at which his disease began is a source of error. Factors of this kind may explain why the histological changes were more advanced in Case 3 than in the two following cases, in which the disease was of longer standing. However, from the case history it appears likely that a more rapid progression of the process may also have been the reason for the pronounced changes in the biopsy tissue in Case 3.

The "degenerative" changes become more pronounced the more advanced the disease. On the whole, the development of nuclear changes and sarcoplasmic degeneration appear to proceed at the same rate, although, as has been seen, either may occur alone. The nuclear changes ("sick" nuclei, pyknotic nuclei, nuclei with haloes) are here considered signs of degeneration. Such nuclei frequently occur in rows or in large groups either hypolemmaly or centrally. Since some authors (Hassin and Dublin,[16e] Lewin,[18] and others) have interpreted such nuclei as belonging to myophages, our reasons for rejecting this view are appropriately given.

The highly hyperchromatic appearance of the nuclei of the allegedly phagocytic cells and their close aggregation (Figs. 12 and 17), leaving no room for their cytoplasm, appears incompatible with the assumption that they are phagocytic. It also seems strange that their cytoplasm should never be visible. Furthermore, if these nuclei belong to phagocytes, it is strange that fibers or parts of fibers having a heavily degenerated sarcoplasm and no myofibrils are frequently found without any invasion by "myophages" (Figs. 16, 19, and 25), whereas the nuclei may be abundant in extremely atrophic fibers showing preserved myofibrils with cross striations. Finally, the macrophages occurring in physiological resorption of muscles of the tadpole tail (personal observation) or in experimentally produced muscular destruction [16g] are of another type.

There is meager evidence for considering the nuclei in question as belonging to myophages. The facts enumerated above are in favor, rather, of their being muscle nuclei in various processes of degeneration. The absence of a convincing picture of cell division does not exclude the possibility that they originate by division of the muscle nuclei themselves.

The "degenerative" changes, as has been seen, may occur in extremely atrophic fibers but are more frequently seen in less atrophic, normal-sized, or hypertrophic fibers. The occurrence of fibers showing sarcoplasmic degeneration in one part and intact structure in an adjoining part (Fig. 21) is particularly striking and indicates that the degenerative process may begin locally in the muscle fiber. Similar findings have been made by Tower [31] in experimental denervation. The "degenerating" part of the fiber is then usually thicker than the other, presumably owing to swelling in the process of degeneration. The looser and more edematous appearance of the surrounding connective tissue when there is sarcoplasmic degeneration than when there is "simple" atrophy (Figs. 6 and 7) may indicate that the degenerative process may set in rapidly, a conclusion supported by the observation that such loose connective tissue is found chiefly around less atrophic, normal-sized, or hypertrophic degenerating fibers. If the atrophy proceeds undisturbed, there seems to be time for the formation of a denser connective tissue. It thus appears that, for an unknown reason, some of the muscle fibers, having lost their innervation, will undergo a slowly progressive atrophy before ultimately degenerating, while others will degenerate relatively early, even before their diameter is clearly reduced. The occurrence in groups of fibers of each type in some cases is noteworthy, although no explanation can be given.

The hypertrophic fibers have been considered by most authors as signs of regeneration—normal fibers trying to compensate. The phenomenon of cleavage might

also be interpreted in this way. Experimental evidence has been presented [34] that atrophic fibers may become reinnervated by nerve fibers of adjoining normal units. Significant hypertrophy of individual muscle fibers has, however, not been noted in these experiments.[34c] The present material does not permit any conclusion as to whether denervated fibers may become reinnervated in progressive neuropathic muscular atrophy. However, the frequent occurrence of degenerative changes in hypertrophic fibers is remarkable and seems to mean either that these fibers are not very viable or that they, in turn, lose their innervation and atrophy.

From a practical point of view, the findings in the present study make clear that biopsy of muscle from patients suspected of having progressive neuropathic muscular atrophy of the Charcot-Marie-Tooth type may be of diagnostic value. Biopsy specimens preferably should be taken from relatively recently affected muscles, since in muscles which have been atrophic for many years the degenerative changes will dominate the picture, and may be mistaken for evidence of a dystrophic process. In progressive muscular dystrophies such changes are much more marked, but the characteristic grouping of fibers in the same stage of atrophy is not seen.

SUMMARY

The histological findings in 20 biopsy specimens of muscle from 14 patients with progressive neuropathic muscular atrophy of the Charcot-Marie-Tooth type are reported. Eight of the patients were reexamined clinically, after periods of up to 11 years.

Reasons are given for considering the clinical diagnosis certain in all cases, and the pedigree of two families are presented (Fig. 2). The mode of inheritance appears to be purely dominant.

In early stages atrophy of muscle fibers in groups is typical (Fig. 3). There are some increase in the hypolemmal nuclei and some increase in connective tissue, but less in adipose tissue. Some fibers are hypertrophic.

In disease of more than four years' duration atrophy of fibers in groups is still present, but less prominent. There are a greater increase in connective tissue and a definite increase in hypolemmal nuclei. Degenerative changes in the nuclei (pyknotic nuclei, nuclei with a halo, "sick" nuclei) become conspicuous, as well as degeneration of sarcoplasm (granulation, vacuolation, cloudy swelling) and disintegration of myofibrils. Structurally preserved but extremely atrophic muscle fibers may, however, be seen even in cases of long-standing disease. Histological details are illustrated by photomicrographs.

The histological findings are compared with those in amyotrophic lateral sclerosis and other progressive muscular atrophies due to diseases of peripheral motor neurons and with those occurring in peripheral nerve injuries in man and animals. It is concluded that the muscular changes in the disease under consideration are due to a disorder of peripheral motor neurons.

34. (*a*) van Harreveld, A.: Re-Innervation of Denervated Muscle Fibers by Adjacent Functioning Motor Units, Am. J. Physiol. **144**:477-493, 1945. (*b*) Hines, H. M.; Wehrmacher, W. H., and Thomson, J. D.: Functional Changes in Nerve and Muscle After Partial Denervation, ibid. **145**:48-53, 1945. (*c*) Weiss, P., and Edds, M. V., Jr.: Spontaneous Recovery of Muscle Following Partial Denervation, ibid. **145**:587-607, 1946.

It appears that the affected muscle fibers may either atrophy slowly and reach a very advanced degree of atrophy (2 to 4μ) with preservation of their cross striations, or they may at a relatively early stage undergo degeneration. The occurrence of degenerative changes does not necessitate the assumption of factors other than denervation as responsible for the muscular changes.

The more frequent occurrence of degenerative changes in the muscle fibers and their nuclei in Charcot-Marie-Tooth atrophy than in other muscular atrophies due to disease of peripheral motor neurons may be explained by the longer duration of the disease, time being available for the late stages of the process to develop.

Muscle biopsies on patients suspected of having the Charcot-Marie-Tooth type of atrophy may be of diagnostic value.

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APPENDIX

Only positive data are included in the following brief abstracts of the histories and clinical findings in the 14 cases studied. When not otherwise stated, the results of special tests and laboratory investigations, to which all patients were subjected, were normal. When no mention is made of familial occurrence of the disease in a case history, positive information on this point was lacking. The date in parenthesis following the initials of the patient refers to the time of his (her) stay in the Neurological University Clinic at which the biopsy specimen was taken. The age of the patient given refers to his (her) age at the time of treatment in the clinic or of examination in the outpatient department.

REPORT OF CASES

CASE 1.—A. S. (January, 1946), a farmer's wife aged 36.

Her father (N. L.) and his brother (M. L.) had been treated in the Neurological University Clinic for progressive neuropathic muscular atrophy of the Charcot-Marie-Tooth type (Fig. 2). Their symptoms started when they were 28 and 43 years, respectively. Her brother is A. L. (Case 5) in this material.

The patient noticed pains in her left calf at the age of 35 and shortly later had weakness in the left calf and foot, followed by progressive muscular wasting of the left calf and thigh. Fasciculations appeared in the left leg, and later in muscles of the other extremities as well.

Clinical examination showed slight diffuse atrophy of the left arm, but definite atrophy of the thenar and hypothenar eminences of the left hand, and of the left leg, particularly the calf and part of the thigh. Muscular power was reduced in correspondence with muscular wasting. The left Achilles jerk was weakened.

Control examination, in June, 1952, showed there had been a steady progression of the disease. The right leg and both arms were affected, and there had been cramps in the calf muscles. The findings were marked atrophy of the intrinsic muscles of both hands, chiefly the left, and of the ulnar part of the forearms; atrophy of both calves, of the left more than of the right, and of the lower two-thirds of both thighs; severe pareses of the legs, so that walking was possible only with one or two sticks; fasciculations in all limbs; slight hypesthesia to cutaneous sensation in both feet laterally; reduction in vibration sense distally in the legs, which were cold and cyanotic; abolition of the knee and ankle jerks bilaterally, and some weakening of the deep reflexes in the arms.

CASE 2.—E. C. (outpatient department, May, 1944), a lieutenant-colonel's daughter, aged 3½ years.

When the child was 1½ years of age, her parents noticed that her lower extremities were weak; in particular there was difficulty in dorsiflexion of the feet. Gradually "drop foot" developed bilaterally.

Clinical examination showed moderate atrophy of the muscles of both calves, more pronounced in the right than in the left, and affecting chiefly the lower parts; reduced power on dorsiflexion of the feet, and absence of knee and ankle jerks bilaterally.

The patient was seen on several occasions during the following years, and her disease was observed to run a steadily progressive course. There are now pronounced pareses and atrophy of both hands.

Case 3.—A. R. (April, 1946), an instructor, aged 43.

The patient's father, who died at the age of 50, had had muscular weakness of both legs as long as the patient could remember. A sister (G. R.) was examined at the outpatient department of the Clinic in 1947, where her disease was diagnosed as progressive neuropathic muscular atrophy of the Charcot-Marie-Tooth type.

From the age of 41 the patient had had a limp in his left leg. His left calf had grown thinner, and about one year after appearance of his first symptoms he noticed weakness in his right leg, particularly on dorsiflexion of the foot.

Clinical examination revealed atrophy of, and corresponding reduction of muscular power in, both calves, involving chiefly the soleus muscle on the left and the peroneal muscles on the right, and hypesthesia to pinprick over the right foot and calf, extending from the first and second toes over the dorsum of the foot approximately to the middle of the lateral side of the calf. The sense of vibration was weaker distally in the right leg than in the left. Ankle jerk was absent on the left and weakened on the right. In December, 1946, the patient reported the occurrence of symptoms which were considered subjective signs of fasciculations. In October, 1947, he complained of a feeling of coldness in his right leg. In October, 1950, the atrophy was found to have increased and to extend proximally to the hip region bilaterally. His gait was then rocking.

Case 4.—S. K. (May, 1943), a foreman's wife, aged 40.

At the age of 37, the patient had onset of pains in the left sole. Approximately one year later her left calf became progressively thinner, and by-and-by weakness of both calves became conspicuous.

Clinical examination showed wasting of the muscles of the left calf and thigh and corresponding muscular weakness. There was no distinct atrophy of the right leg, but reduced power was evident on dorsiflexion of the right foot. The ankle jerk was abolished on the left and weakened on the right.

The control examination, on June, 1952, revealed that since her stay in the Neurological Clinic, in 1943, her disease had run a steadily progressive course, her right leg being as severely affected as the left. Since 1946 there had been progressive wasting of the intrinsic muscles of the hands, and later of the muscles on the ulnar side of the forearms also, with some involvement of the upper arms. In 1947 she had to use crutches when walking, and after a fracture of the collum femoris, in December, 1948, she had been confined to a rolling chair.

Examination revealed marked atrophy and loss of power in the intrinsic muscles of both hands, somewhat less advanced atrophy on the ulnar side of both forearms, and considerable paresis of movements in the elbow joints and some paresis of movements in the shoulder joints. There was considerable edema of both legs, concealing possible atrophy, but both legs were almost paralyzed except for some movement in the hip joints. There were hypesthesia to cutaneous sensation on the lateral side of the feet and the lower third of the calves and reduced vibration sense distally. Both legs were cold and cyanotic. All tendon reflexes were abolished. Fasciculations were present in the arms and legs.

Familial Occurrence (Fig. 2).—When she was admitted to the ward of the clinic in 1943, the patient said no members of her family were affected with the same disease. However, when seen again, in 1952, she stated that since her stay in the Clinic two of her sisters had become affected with the same disease; furthermore, she had obtained information that her maternal grandfather had probably also suffered from it. The latter (O. G., Fig. 2), who died at the age of 57, had had trouble in walking since he was 40 and had been unable to walk the last

years of his life. Her grandfather's mother was a sister of one of the ancestors of another family of which four members had been treated in the Neurological University Clinic for progressive neuropathic muscular atrophy. Two of them are A. S. and A. L. (Cases 1 and 5 in this material). The two others are the father of these two patients and his brother (N. L. and M. L., Fig. 2).

The two sisters of S. K. (Case 4) were examined by one of us (A. G. F.) in June, 1952. The elder sister, G. H. B., born in 1900, at the age of 45 noticed weakness in her right foot, which spread by and by to the whole leg. During the last few years there had been loss of power also in both arms, painful cramps, and fasciculations. The feet and hands tended to be cold and blue. Clinical examination revealed pronounced atrophy and corresponding weakness distally in both arms, severe paresis of the right leg, fasciculations in the interosseus muscles of the right hand, and doubtful hypalgesia over the lateral side of the dorsum of the right foot. The tendon reflexes were weakened in both upper extremities. The ankle jerks were abolished.

The younger sister, E. S., born in 1904, had noticed the beginning of her disease at the age of 41. On clinical examination, her symptoms were found to be very much like those of her sisters, and the diagnosis of progressive neuropathic muscular atrophy was clear.

Case 5.—A. L. (March, 1944), farm laborer, aged 31.

His father and uncle had been treated in the Neurological University Clinic for progressive neuropathic muscular atrophy (N. L. and M. L.; Fig. 2). His sister is A. S. (Case 1 of this report). The patient noticed onset of his disease at the age of 27, when he began to limp slightly. One or two years later his left leg grew weaker, and there was wasting of the left calf and thigh.

Clinical examination showed considerable wasting of the muscles of left thigh and calf and of the right calf. There were pareses corresponding to the atrophy. No convincing evidence of sensory loss was noted. The knee jerks were weakened and the ankle jerks abolished.

The control examination, on June, 1952, showed that there has been a steady progression in his disease. In 1948-1949 he noticed weakness of both hands, and later of the forearms. At the time of the last examination, he was able to walk only with difficulty. Examination revealed atrophy of the muscles of both hands; considerable atrophy of the forearms, chiefly on the ulnar side; some atrophy of the upper arms; distinct atrophy of the muscles of the calf, of the left more than of the right, and some atrophy of the lower part of the thighs. There was weakness corresponding to atrophy. Fasciculations were present. There was hypesthesia to cutaneous sensation laterally on the dorsum of both feet; the sense of vibration was lost distally in the feet. The knee and ankle jerks and the biceps and triceps reflexes were abolished.

Case 6.—B. E. (May, 1945), a carpenter's wife, aged 42.

The patient was a niece of G. O. (Case 7). For information on the heredity, see the report on Case 7. Since the age of 38 her left leg had become thinner and weaker. About a month prior to admission to the Clinic she had noticed peculiar sensations, described as prickings, (fasciculations?) on the lateral aspect of the left thigh on exertion, and some cramping in her left calf had occurred.

Clinical examination showed considerable muscular atrophy of the left leg, most pronounced in the calf but also prominent in the lower third of the thigh, with some indication of a circular upper border. There was muscular weakness corresponding to the atrophy. No convincing atrophy of the right lower extremity was noted, but there was clear-cut reduction of power on dorsiflexion of the big toe and foot. The left foot and calf were somewhat cold and cyanotic. The left knee jerk was weakened; the ankle jerks were abolished. Deep reflexes in the upper extremities were weak.

Case 7.—G. O. (December, 1944), a shop-girl, aged 53.

The patient's father was said to have suffered from muscular wasting from the age of 44 until he died, at 58. One of her four sisters had had muscular wasting for 23 years, since the age of 30. B. E. (Case 6) was a niece of the patient. The patient's symptoms started when she was 45 with weakness of her right foot. By and by muscular power decreased in both legs, the right being weaker than the left. In 1944 she could walk only about 200 meters at a time. She had had cramps in both calves and had noted fasciculations.

Clinical examination revealed considerable loss of muscular power in both legs, increasing distally. On account of ample subcutaneous fat and edema, the determination of muscular atrophy was uncertain. There was some diminution of joint sense in the big toes. Knee jerks were very weak; ankle jerks were abolished. The legs were cyanotic.

Case 8.—T. A. (July, 1941), an engineer, aged 27.

The history and clinical findings in this case have been fully reported in the paper by Brodal and Refsum.[3] There were atrophy and loss of power distally in all four extremities, fascicular twitchings, hypesthesia to superficial sensation of all types distally in both legs and arms, and reduction of vibration sensibility. The ankle jerk was absent on both sides. There was some cyanosis of both feet and hands. Talipes cavus was present bilaterally. Frequent cramps occurred in both legs.

Case 9.—P. S. (February, 1943), tramway driver, aged 47.

The patient had first noticed weakness in his legs and paresthesias in both soles 10 to 15 years prior to admission. Later he had progressive loss of power of both legs. Recently he had noted some loss of power and reduced superficial sensibility on the ulnar side of both hands and in the fingers of the ulnar innervation.

Clinical examination showed muscular atrophy of the upper extremities distally, of the anterior tibialis muscle group bilaterally, and of the medial side of the right thigh. Pareses corresponded to the atrophy. Fasciculations were present in the legs and arms. There was hypesthesia to all types of superficial sensation distally in all four limbs. Vibration sense was reduced distally in both legs. The deep reflexes were weak.

Case 10.—W. P.-P. (May, 1948), an agent's daughter, aged 29.

The patient's father is O. P.-P. (Case 14) of this study. When she was 7 years old, her parents noticed that her legs were weak and that she had difficulty in running. Since November, 1946, there had developed weakness also in both arms.

Clinical examination revealed marked atrophy distally of the muscles of both calves, particularly the peroneal group, and of the intrinsic muscles of both hands and the lower half of both forearms, with rather distinct proximal borders. Muscular power was correspondingly reduced. The deep reflexes were severely reduced in both arms and absent in both legs. Fasciculations were present in both legs.

The control examination, in June, 1952, revealed that there had been a slow but steady progression of the disease since 1948. There were severe loss of power in the quadriceps femoris muscle and increased pareses of the calves and arms. The hands and feet were cold and moist; the feet and the distal part of calves were cyanotic. Vibration sense was impaired, and was almost abolished distally in all four extremities. The deep reflexes were all absent except for the radial response.

Case 11.—J. L. (October, 1944), a works manager, aged 55.

At the age of 32 the patient noticed weakness in his left calf and had some pain. The weakness increased gradually in the following years and was accompanied with muscular wasting. Somewhat later his right calf was affected in the same manner, but less severely. Occasionally he had cramps in the left leg.

Clinical examination revealed marked atrophy of the left leg and the lower part of the left thigh, with a rather distinct circular upper border between the lower third and the upper two-thirds of the thigh (Fig. 1*A*). There was bilateral talipes cavus (pes excavatus). There were loss of power corresponding to the muscular wasting and slight paresis of the right leg. Fasciculations were occasionally seen. There was slight hypalgesia on the lateral side of the left calf and foot. The knee jerks were weak, particularly the left; the ankle jerks were absent.

The control examination, in November, 1951, revealed deterioration. There were then atrophy of the right calf as well, slight hypesthesia to touch in the hypalgesic area in the left leg, and abolition of the left knee jerk, with the right knee jerk barely elicitable.

Case 12.—H. A. (July, 1944), a sailor, aged 58.

Since 1915 the patient had tired easily in both legs, particularly the left. He was first admitted to the ward of the Neurological Clinic in 1922. Examination then showed distinct atrophy of both calves, chiefly the peroneal muscles; some atrophy of the muscles of the thighs, and very slight atrophy of the muscles of the hands and forearms. Pareses corresponding to the atrophy were present. Since 1939 he had been unable to work.

Clinical examination in 1944 revealed considerable atrophy of both legs approximately to the transition between the middle and the lower third of the thigh, and distinct atrophy of the muscles of the hands and forearms. There were pareses corresponding to the atrophy. Vibration sense was somewhat reduced in both legs. The deep reflexes in the arms were weak, as were the knee jerks; ankle jerks were absent. There was moderate pes excavatus bilaterally.

CASE 13.—A. B. (March, 1952), a worker, aged 59.

Since the patient had typhoid, at the age of 22, there had been slowly progressive wasting and loss of muscular power in both legs. There had also been some impairment of power in the hands and arms.

Clinical examination showed severe muscular wasting of both legs, with a rather abrupt transition to apparently normal muscles at the border between the lower and the middle third of each thigh (Fig. 1*B*). Muscular power was correspondingly reduced. Fasciculations were occasionally seen. The right hand showed moderate, but clear-cut, paresis and atrophy of thenar eminence (Fig. 1*B*) and the radial interosseus muscles. Some reduction of cutaneous sensibility was noted distally in all four extremities, which were cold and cyanotic. The knee jerks were weak; the ankle jerks were absent; there was slight pes excavatus.

CASE 14.—O. P.-P. (outpatient department; September, 1944), an agent, aged 64.

The patient, the father of W. P.-P. (Case 10), considered himself healthy. He was called up for control examination in the outpatient department when his daughter was found to have progressive neuropathic muscular atrophy.

Clinical examination revealed that the lower halves of both calves were remarkably thin, as compared with the well-developed muscles of the upper halves. There was a rather sharp, almost circular, transition. Gait was natural. No pareses or other atrophy could be found. Fasciculations occurred in the anterior tibialis muscle group and in the triceps surae. The diagnosis of a rudimentary type of progressive neuropathic muscular atrophy was made.

On control examination, in June, 1952, the patient stated that he had suffered from cramps in his calves for six to eight years and that his legs had become weaker. His legs appeared almost as they had in 1944, but the left anterior tibialis muscle group seemed to be more atrophic. Power on supination, pronation, and dorsiflexion of the left foot was distinctly reduced. Fasciculations occurred in the muscles of both calves. There was hypesthesia to touch and pain on the lateral side of the dorsum of the foot and the lower part of the calf bilaterally, but chiefly on the left side. Vibration sense was reduced over the lateral malleoli, chiefly the left. The ankle jerk was weakened bilaterally, particularly on the right.

STUDIES ON BLOOD-BRAIN BARRIER WITH RADIOACTIVE PHOSPHORUS

III. Embryonic Development of the Barrier

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SHORTLY after the discovery was made that the central nervous system cannot be stained by intravenous injection of vital dyes and the concept of a blood-brain barrier was established, the question arose: Does or does not this barrier exist at birth? The phenomenon of kernicterus seemed to indicate that in the newborn infant the barrier is not yet fully developed, and experiments with vital dyes in young animals gave some support to this inference. The evidence these experiments offered was not certain, however. Moreover, some of these early investigations yielded contradictory results. It was thought that the application of radioactive phosphate would clarify the matter of the development of the blood-barrier and also reveal whether or not a similarity exists, in the intrauterine and the early postnatal stage, in the permeability of the barrier to pigments (bilirubin), vital dyes, and ions (P^{32}). The analogy between the response of the brain in adult men and that in mammals to acid vital dyes and P^{32} has been shown previously.[1]

MATERIAL AND METHODS

For the experiments described here, I selected rabbits, since it was important to have a laboratory animal which was easily propagated and with a large enough brain for isolated examination, even in the embryonic stage. Another important requirement was that the animal have a hemochorial type of placenta, which has the same characteristics as the human placenta and, also, the fastest ion-transfer rate. The rabbit placenta, however, may in the later stages of pregnancy undergo changes in becoming hemoendothelial in character (Mossman[2]). The gestation period in the rabbit is 31 (30 to 32) days.

Altogether, 14 animals were used, 5 of them being pregnant. They were killed at various ages—at the third to the fourth week of pregnancy; at birth, and at one, two, four, five, and seven weeks after birth. Of the pregnant rabbits, two were killed between the third and the fourth week of pregnancy; two, between the fourth week and full term, and the fifth, at full term. Study was made of six fetuses from the first of these groups and of four fetuses from the other two groups. According to the stage of pregnancy, the lengths of the fetuses were 8.5, 9.2, 10.5, and 11.0 cm. and the weights, 17, 18, 62, 64 gm., respectively. The newborn rabbits were 12.5 cm. long and weighed 66 gm. They were born 24 hours after the administration

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1. Bakay, L.: Studies on the Blood-Brain Barrier with Radioactive Phosphorus, A. M. A. Arch. Neurol. & Psychiat. **66**:419-426, 1951; Studies on Blood-Brain Barrier with Radioactive Phosphorus, II. Hypophysis and Hypothalamus in Man, ibid. **68**:629-640, 1952.

2. Mossman, H. W.: Rabbit Placenta and the Problem of Placental Transmission, Am. J. Anat. **37**:433-497, 1926.

of P^{32} to their mothers. The adult rabbits consisted of the five pregnant animals and four controls. To obtain a uniform base line of P^{32} concentration in the blood, brain, and various other organs, each animal was given a single dose of P^{32}, ranging from 100 to 250 μc, injected parenterally 24 hours before death. The animals were killed by heart puncture and air embolus. Removed at once and stored at a temperature of —20 C. were blood samples and various organs, i. e., the whole brain, lungs, liver, spleen, kidneys, and pectoral muscle. In the pregnant rabbits the fetus and its corresponding organs were removed, as well as the uterus and placenta. In the smaller fetuses the blood was taken from the heart after this organ was frozen. In a few cases radioautographs of sagittal or transverse sections of the brain or of the entire head were prepared on Kodak No-Screen X-ray Film. In all cases pieces of various parts of the brain and other organs were placed on aluminum planchettes and weighed, dried, and counted for radioactivity by scalers. The final data were computed in counts per minute per milligram of fresh tissue. The P^{32} content of whole blood was taken for a base line, slight corrections being made from case to case in order to compute all data to this standard. In addition, to obtain data in terms of specific activity, total phosphate determinations were made on the examined parts of the brain, liver, and whole blood, as well as the serum.

RESULTS

After correcting the P^{32} content of the various organs by computing the data to a standard concentration of the tracer in the whole blood (the standard being taken arbitrarily as containing 1 count per milligram of blood per minute, 24 hours after the injection), one can easily demonstrate that the P^{32} content of the brain of adult animals is 25% (20 to 40%) of the concentration in the blood, with relatively little variation. This figure gives a reliable basis for a comparison of the accumulation of radioactive phosphate in the fetus and young animal, on the one hand, and that in the adult, on the other.

It appears also that the uptake of P^{32} by the brain is more regular than that of other organs and that the concentration of P^{32} in the parenchymatous organs undergoes wider variations. It would have been more exact to determine the concentration of the isotope in the plasma and use this as a base line. However, the separation of the serum from the red blood corpuscles could not be carried out to my satisfaction in the young fetus, in which the whole blood usually had to be removed from the isolated heart after it had been frozen.

Thus, if the P^{32} concentration of the blood of each individual animal is taken as 1 count per milligram per minute (in the fetus the correction was made to the blood of the fetus, and not to the blood of the mother), the determinations show a higher uptake of the tracer by the embryonic and very young brains than by the brains of older animals (Fig. 1). The tracer deposit is greatest in the central nervous system of the fetus and newborn rabbit, where it actually surpasses the blood level. In the younger fetus the brain contains about six times the amount of the tracer found in the adult animal. This ratio drops to about 4:1 shortly before term, only to rise again somewhat in the newborn rabbit. It is questionable whether or not this drop in concentration before delivery is related to a sudden decrease in the placental permeability at this stage.

The cerebral concentration of P^{32} remains high in the first few postnatal weeks, although it decreases steadily. Almost normal concentrations can be obtained four weeks after birth, and at seven weeks no difference can be found between young and mature animals.

If the same data are given in terms of specific activity (counts per milligram per minute / total phosphate content per milligram of tissue), the time-concentration

curve of the brain follows essentially the same pattern, although there is a slight change in the shape of the curve (Fig. 1). This change is due to the fact that the average total phosphate content of the brain is less in the fetus and young animal than in the adult. The determinations revealed a mean phosphate concentration of 180 mg. per 100 gm. in the fetus between three and four weeks, 222 mg. in the fetus between four weeks and term, 226 mg. in the newborn rabbit, and the same amount (220 to 230 mg.) in young rabbits up to 5 weeks of age. Thereafter the level increases rapidly, and at the age of 7 weeks it is already 282 mg. per 100 gm. which is the lower limit of that found in the normal adult (280 to 320 mg. per 100 gm.).

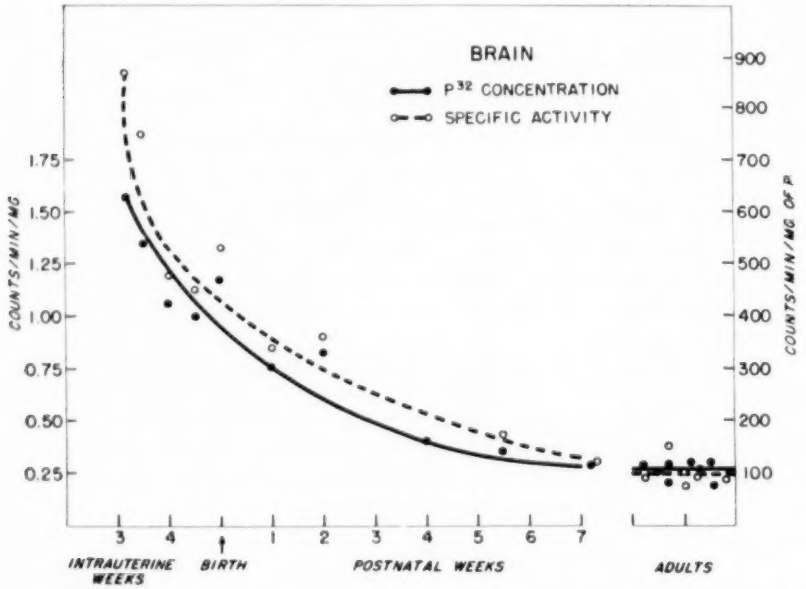

Fig. 1.—Cerebral P^{32} concentration (solid line) and specific activity (line of dashes) of rabbits of different ages, 24 hours after parenteral injection of the tracer.

It is interesting to compare the P^{32} uptake by the brain with that noted in the liver, which, in absolute values, shows very little variation with age (Fig. 2). Neither is there much variation in the specific activity. The liver of adult rabbits contains an average of 300 mg. of total phosphate per 100 gm., as compared with 260 mg. per 100 gm. for the 3-week-old fetus. Consequently, the ratio between the P^{32} content of the liver and that of the brain steadily changes with time from 6:1, at the third week of pregnancy, to 20:1 or 35:1, in older animals (Fig. 3).

The same difference was found between other parenchymatous organs, muscle, etc., and the brain. There is not much difference between the phosphate turnover of embryonic, or young, and older tissues of some organs. Other organs, such as the lung, kidney, and spleen, show an increase from the time of birth (Fig. 2). The behavior of the brain and the decrease of its P^{32} concentration with time are, as far as I am able to tell, unique.

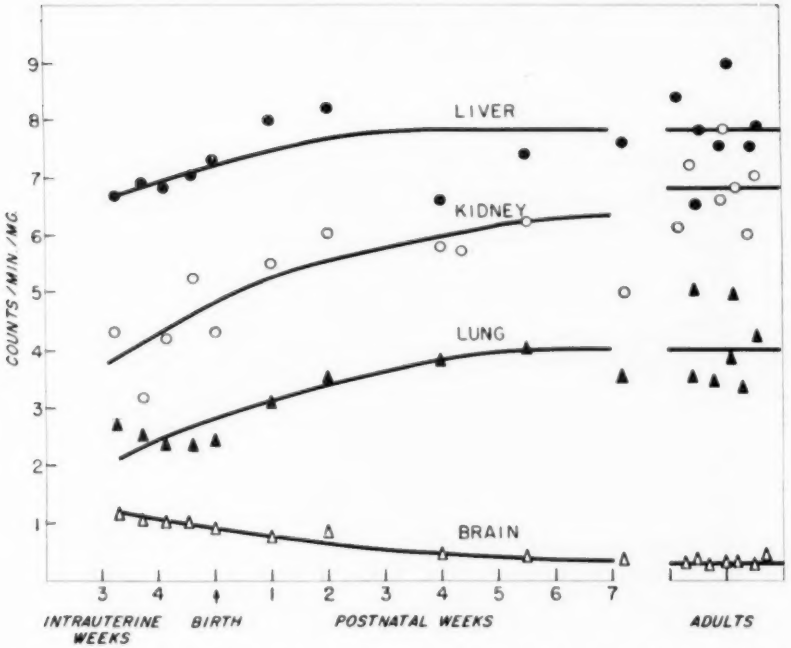

Fig. 2.—P^{32} concentration in various organs of fetal, young, and adult animals 24 hours after the injection.

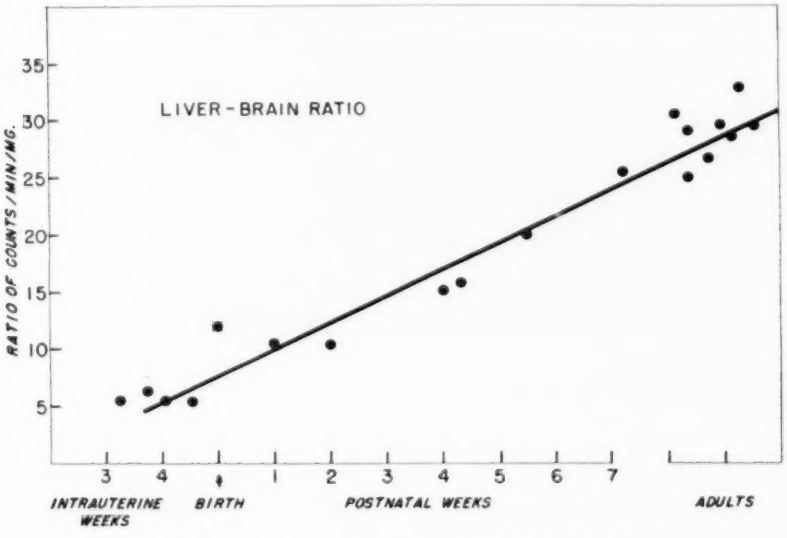

Fig. 3.—Liver-brain ratio of P^{32} in various age groups.

Despite the fact that the embryonic and early postnatal brain concentrates considerably more P^{32} than does the adult brain, its uptake is still low when expressed in absolute values and compared with any of the other tissues. Radioautographs of sections of the whole body or head of the fetus, exposed for various lengths of time, clearly illustrate this point (Fig. 4). Yet, radioautographs of cross sections of the

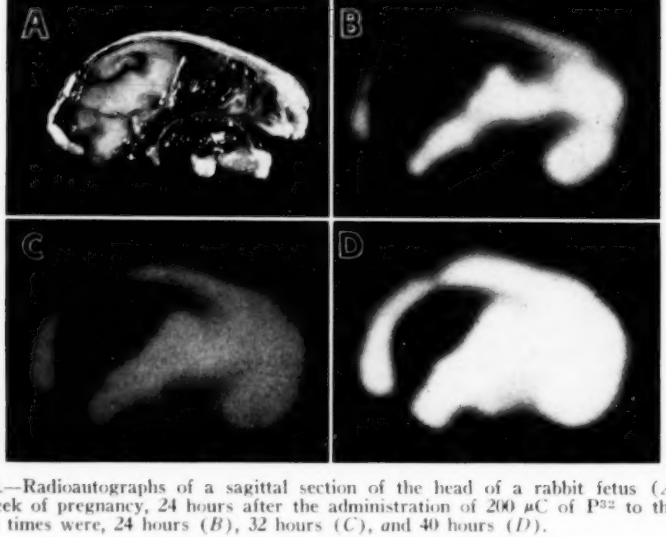

Fig. 4.—Radioautographs of a sagittal section of the head of a rabbit fetus (*A*) in the fourth week of pregnancy, 24 hours after the administration of 200 μC of P^{32} to the mother. Exposure times were, 24 hours (*B*), 32 hours (*C*), and 40 hours (*D*).

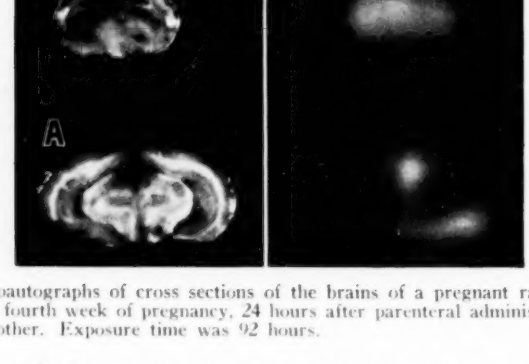

Fig. 5.—Radioautographs of cross sections of the brains of a pregnant rabbit (*A*) and its fetus (*B*) in the fourth week of pregnancy, 24 hours after parenteral administration of 200 μC of P^{32} to the mother. Exposure time was 92 hours.

fetal and maternal brains, on the other hand, prepared on the same film and exposed and developed under identical circumstances, show a difference not only in the amount of tracer but also in its deposits (Fig. 5). The distribution of P^{32} in the brain of the fetus is almost uniform, whereas in the brain of the mother it concentrates mostly in the choroid plexuses and in the lining of the ventricles, and much less in the nerve tissue proper. I take these findings as an indication that even

in the fetus there exists a barrier for P^{32} between the blood and central nervous system, but the permeability of this barrier is greater than in adults. In rabbits, it decreases steadily with time and becomes completely developed about seven weeks after birth.

Table 1 shows the distribution of P^{32} in the blood, brain, and other organs of the pregnant rabbit, the fetus, and the newborn rabbit. It shows, also, an exact correlation between the P^{32} concentration of the blood and that in the brain in the fetus and the newborn. Comparative values for the maternal and the fetal blood show some decrease in the rate of placental transfer of P^{32} shortly before delivery.

COMMENT

The theory concerning increased permeability of the blood-brain barrier in infants was derived from clinical observations. The phenomenon of kernicterus in newborn infants appeared to offer irrefutable proof of this theory, showing in the

TABLE 1.—*P^{32} Content of Various Organs of Pregnant Rabbits and Their Fetus**

	Blood	Liver	Lung	Kidney	Brain
1. Mother	1.0	7.5-8.0	5.5	6.9	0.26-0.29
Fetus (8.5 cm.)	1.3-1.4	8.2-9.9	3.8	6.0	1.56-1.64
%	130-141	102-132	69	87	540-630
2. Mother	1.0	9.0	5.2	7.8	0.23-0.36
Fetus (9.2 cm.)	1.40	9.5	3.5	4.3	1.35-1.41
%	140	105	67	55	370-600
3. Mother	1.0	6.8-8.1	3.2	6.1	0.40
Fetus (10.5 cm.)	1.1	6.8	2.3	4.3	1.10
%	110	84-100	72	70	275
4. Mother	1.0	6.5	2.9	6.6	0.24-0.25
Fetus (11.0 cm.)	0.6	3.8-4.7	1.25	3.3	0.54-0.65
%	60	58-72	43	50	216-270
5. Mother	1.0	8.4	3.5	7.2	0.31-0.38
Newborn (12.5 cm.)	0.6	4.6	1.5	2.7	0.46-0.54
%	60	55	43	38	121-174

* Values are expressed in counts per minute per milligram of tissue.

early postnatal stage a passage of bilirubin from the blood to the nuclear gray matter of the brain and into the cerebrospinal fluid, whereas such pigment could not, on the other hand, be recovered from the brains of icteric adults. Interestingly enough, this early observation is still one of the very few bits of direct evidence in this respect. Its value is limited by the fact that the exact mechanism involved in the development of kernicterus is still unknown. Although the increased permeability of the fetal and early postnatal blood-brain barrier has been generally accepted and instances have frequently been noted, the number of such investigations is very small, and the findings are often controversial. Behnsen,[3] carrying out experiments with trypan blue in mice, compared the concentration of this dye in the cerebral tissue of young animals with that of adults, after single or repeated intravenous administration. At that time it was already known that some part of the central nervous system (pituitary, pineal gland, tuber cinereum, choroid plexus, etc.) could be stained with intravenous injection of trypan blue. Behnsen was able to demon-

3. Behnsen, G.: Über die Farbstoffspeicherung im Zentralnervensystem der weissen Maus in verschiedenen Alterszustanden, Ztschr. Zellforsch. u. mikr. Anat. **4**:515-560, 1927.

strate that the areas that took the dye were relatively much larger in newborn and young mice than in older ones and concluded that the permeability of the barrier is locally increased at an early stage of life. Although frequently misquoted, Behnsen's conclusions do not reveal a generalized increase in the permeability of the barrier. Näätänen [3a] used methylene blue, injecting it parenterally into several nonviable human fetuses and newborn infants who died shortly after birth of congenital anomalies. His specimens showed some signs of increased permeability, but in the absence of adult controls one cannot evaluate his findings. Broman,[4] using his trypan-blue technique in various animals, was not able to demonstrate any relevant differences among old, fully grown, and newborn animals.

Thus, the generally accepted theory of the increased permeability of the fetal blood-brain barrier remained unconfirmed. Yet there were physiological reasons for assuming an increased permeability. It was pointed out that the placenta is able to perform the function of the fully developed blood-brain barrier by keeping certain substances from entering the fetal circulation. This hypothesis, however, has not been confirmed by modern investigations.

Flexner and his co-workers made important observations on the placental transfer of various tracers. Using Na^{24} in different animals at various stages of gestation, they found that the rate of transfer of sodium per gram of placenta increases in each animal as gestation proceeds until just before term, when there occurs a sharp decrease, corresponding to morphological changes in the placenta (Flexner and Gellhorn [5]). Similar observations were made in humans: The transfer of both sodium (Flexner, Cowie, Hellman, Wilde, and Vosburgh [6]) and water (Hellman Flexner, Wilde, Vosburgh, and Proctor [7]) reached its peak at the 35th week of gestation, declining rapidly thereafter. It was also demonstrated that the rate of transfer depends upon the morphological structure of the placenta. The smaller the number of tissue layers between the maternal and the fetal circulation, the greater the rate of transfer. Consequently, the transfer was much faster in animals with hemochorial placentas than in those with endotheliochorial, syndesmochorial or epitheliochorial placentas. In the latter types of placenta the outer layer of the chorion is separated from the wall of the uterus by endothelium, connective tissue, and epithelium, respectively. Flexner and Gellhorn [5] found a correlation between the supply transferred to a unit weight of fetus and the rate at which that unit weight of fetus was growing. They concluded that the principle of placental func-

3a. Näätänen, E.: Über die Speicherung der intravenös injizierten Methylenblaulösung im Zentralnervensystem des menschlichen Fetus, Acta Soc. Med. Fenn. "Duodecim." **24**:1-11, 1944.

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5. Flexner, L. B., and Gellhorn, A.: The Comparative Physiology of Placental Transfer, Am. J. Obst. & Gynec. **43**:965-974, 1942.

6. Flexner, L. B.; Cowie, D. B.; Hellman, L. M.; Wilde, W. S., and Vosburgh, G. J.: Permeability of the Human Placenta to Sodium in Normal and Abnormal Pregnancies and the Supply of Sodium to the Human Fetus as Determined with Radioactive Sodium, Am. J. Obst. & Gynec. **55**:469-480, 1948.

7. Hellman, L. M.; Flexner, L. B.; Wilde, W. S.; Vosburgh, G. J., and Proctor, N. K.: Permeability of the Human Placenta to Water and the Supply of Water to the Human Fetus as Determined with Deuterium Oxide, Am. J. Obst. & Gynec. **56**:861-868, 1948.

tion is such that the rate at which a physiologic substance is transferred to the fetus parallels the relative growth rate of the fetus.

The permeability of the guinea pig placenta (hemochorial type) to inorganic phosphate was studied by Wilde, Cowie, and Flexner,[8] who found that transfer rate of P^{32} per unit weight of placenta increased continuously during the observed second half of gestation. However, unlike sodium and water, which are supplied to the fetus in great excess, inorganic phosphate reached the fetus from the maternal circulation in an amount equal only to the total phosphate retained in growth.

The application of radioactive tracers, notably P^{32}, revealed interesting differences in the phosphate uptake by the brains of animals of various ages. Fries and Chaikoff [9] discovered that in rats the uptake of P^{32} per whole liver, kidney, skeletal muscle, and blood remained constant or increased somewhat as the animal grew larger, whereas in the brain the uptake was greatly reduced. They also compared the P^{32} contents of various parts of the central nervous system in rats of different ages, 24 and 48 hours after administration of the tracer.[10] The highest P^{32} recovery in all divisions of the central nervous system was made on the day of birth. From birth until the time the rat attained a weight of 50 gm. P^{32} recovery throughout the brain declined rapidly. As growth proceeded beyond 50 gm., the decline continued, but at a much slower rate.

Stern and Marshall [11] compared the P^{32} content of the fetal brain (stage of pregnancy unknown) with that of the mother in three cats. Twenty-four hours after administration of the isotope, the fetal brain tissue showed small differences in assay as compared with the maternal tissue; 45 and 48 hours after injection the dry-weight values of the fetal brains rose to 2.5 or 4.0 times the values for the maternal brain.

It was necessary, mainly because of my embryonic material, to restrict our experiments to a comparison of the brains of the various animals at one given time, 24 hours after the administration of the tracer. It is known, however, that the blood-brain barrier cannot be explained in absolute figures, but can be described only in terms of time-concentration curves and by comparing the P^{32} content of the blood and brain at various intervals after injection of the isotope. The present experiments showed that the brains of fetuses and young animals one day after injection concentrate much more P^{32} than do the brains of older animals. This means that the young central nervous tissues exchange phosphates faster than the older ones do. It might also indicate that the cerebral time-concentration curve of P^{32} is different in young animals than in adults, reaching its peak soon after the injection (within 24 hours), whereas it takes several days in adults. These data could be explained by assuming that a large concentration of P^{32} in fetal and postnatal

8. Wilde, W. S.; Cowie, D. B., and Flexner, L. B.: Permeability of the Placenta of the Guinea Pig to Inorganic Phosphate and Its Relation to Fetal Growth, Am. J. Physiol. **147**:360-369, 1946.

9. Fries, B. A., and Chaikoff, I. L.: Factors Influencing Recovery of Injected Labeled Phosphorus in Various Organs of the Rat, J. Biol. Chem. **141**:469-478, 1941.

10. Fries, B. A., and Chaikoff, I. L.: The Phosphorus Metabolism of the Brain as Measured with Radioactive Phosphorus, J. Biol. Chem. **141**:479-485, 1941.

11. Stern, W. E., and Marshall, C.: Distribution of Radioactive Phosphorus in Normal and Diseased Brain Tissue: Experimental and Clinical Observations, Proc. Soc. Exper. Biol. & Med. **78**:16-20, 1951.

brains corresponds to and equals the concentration in adults at a later time after the injection. This assumption, however, can be ruled out by the data of Fries and Chaikoff,[12] who found that the time-concentration curves of P^{32} in the rat brains were similar in shape, and that the difference between young and old animals was mostly quantitative.

At any rate, the cerebral vascular permeability for P^{32} is increased in the fetus, and there is hardly any difference between the radioactive phosphate content of the choroid plexus and that of the brain, a striking contrast to the situation in adults.

The transfer and distribution of radioactive phosphate in the human fetus can be demonstrated, briefly, on the basis of the necropsy data in a clinical case.

M. C., a woman aged *32*, in the fifth month of pregnancy, had onset shortly before admission to the hospital of rapidly increasing signs of high intracranial pressure. She was given a single intravenous injection containing *2* mc. of P^{32} to help localize the tumor; six hours later, I performed a craniotomy and removed a single metastatic tumor, the size of a small apple, from the right parietal lobe. The patient did not regain consciousness; her vital signs became gradually weaker, and she died of circulatory failure on the third postoperative day, 80 hours after the administration of P^{32}. Autopsy revealed an undifferentiated malignant tumor of the ovary with metastases to the brain. The pregnancy was verified; the fetus, *20* cm. in length, showed moderate signs of maceration.

TABLE *2.—Distribution of P^{32} in Various Organs of a Woman and Her 5-Month-Old Fetus**

	Mother	Fetus	Percentage
Liver	116	45	39
Abdominal muscle	47	13	28
Hypophysis	73	14	19
Cerebrum	3.0	3.2	107
Cerebellum	3.0	4.8	160

* Values are expressed in counts per minute per milligram of tissue.

The distribution of the tracer in some of the organs of the mother, as well as in the fetus, is summarized in Table *2*.

In evaluating these data, several factors are to be considered. It is obvious that from an experimental point of view they are of limited value. Owing to the inevitable circumstances, we cannot determine the length of time during which this fetus collected its P^{32} from the maternal blood, since we have to assume that it died some time before the mother. Nor de wo know how the macerated conditions of the fetus affected the radioactive phosphate concentrations of the individual organs. Nevertheless, these data are reconcilable with the experimental findings in the rabbit fetus and might very well represent the true status of the blood-brain barrier in a 5-month-old human fetus.

What, then, is the exact meaning of these findings? In attempting to give a single explanation, one is confronted with two alternatives: 1. In embryos and young animals the blood-brain barrier is more permeable. The capillary wall is not yet fully developed, and ions "leak through" to a greater extent. By the time the animal is several weeks old, the capillary wall gradually becomes tight and the blood-brain barrier fully resumes its protective role. *2*. The different rate of phosphate uptake derives from the increased metabolism and faster turnover of the developing nervous system. It is true that the behavior of the brain is unique in this respect and does

12. Fries and Chaikoff, footnotes 9 and 10.

not show any resemblance to the other developing organs of the fetus. On the other hand, the difference in the phosphate metabolism in the fetal, young, and adult brains could be explained by the process of myelination. The appearance of myelin, with its slowly metabolizing phospholipids, might very well correspond to the decreased rate of phosphate turnover of the brain.

I do not find any single explanation satisfactory; a combination of the two possibilities may provide the answer, however. The blood-brain barrier cannot be a simple screening agent but, rather, is a functional part of the central nervous system, even when located in the capillary wall. Its development shows how it is functionally adapted to the needs of the nervous system.

SUMMARY

The concentration of P^{32} in the blood, brain, and other organs was determined in rabbits 24 hours after a single parenteral injection of the isotope.

Five of these animals were pregnant (third week of gestation to full term). The other animals varied in age from 1 to 7 weeks to adulthood.

The turnover of P^{32} was found to be faster in the fetal and young brain than in the adult organ. The cerebral exchange rate of the isotope decreased gradually with time, reaching adult values at the seventh posnatal week. A basic difference was demonstrated with age in the changes of turnover rate between the central nervous system and other parenchymatous organs.

The findings indicate the existence of a blood-brain barrier for P^{32} even in the fetus. However, the permeability of this barrier is greater in the fetus and the young animal than in the adult.

A human case is presented in which the P^{32} concentrations of the maternal and fetal organs are compared.

The placental transfer of various tracers and the metabolism of the fetal brain are discussed with special regard to the concept of the blood-brain barrier.

CLINICAL SIGNIFICANCE OF SCLEROSIS OF THE CORNU AMMONIS

Ictal "Psychic Phenomena"

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AND
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SAN FRANCISCO

IN A LECTURE delivered in 1927, Spielmeyer [1] referred to sclerosis of the cornu ammonis as "this often-described, yet hitherto enigmatic, phenomenon." This statement is still true, even though the pathogenesis of the phenomenon has since been elucidated to a great extent by Spielmeyer himself and his associates. The first gross description of this lesion is generally credited to Bouchet and Cazauvieilh,[2] who, in 1825, observed changes of sclerosis or softening in the hippocampus of epileptic as well as of nonepileptic psychopathic patients. The first microscopic examination was done in 1880 by Sommer,[3] who found the changes to be restricted to the band of pyramidal cells of the hippocampus. The latter area has since been called "Sommer's sector." In 1889 Chaslin [4] described a marginal gliosis in cases of epilepsy and regarded sclerosis of the cornu ammonis as representing merely a site of predilection for such gliosis. Bratz [5] in 1899 confirmed Sommer's findings but noted that the end-plate was as often affected as Sommer's sector and that a part of the dorsal cell band was resistant in many cases. He found that of 50 cases of "idiopathic" epilepsy, sclerosis of cornu ammonis existed in 25, and he noted the same lesion in other diseases associated with convulsive disorder.

What symptoms, if any, might appear as the result of sclerosis of the cornu ammonis has remained obscure. Since the relation of so-called psychomotor epilepsy to the temporal lobe has recently become a problem of major interest in neuropsychiatry, the possible role of the hippocampal formation and its sclerosis in this particular form of epilepsy has been suggested by several authors (Jasper and

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3. Sommer, W.: Erkrankung des Ammonshorns als aetiologisches Moment der Epilepsie, Arch. Psychiat. **10**:631-675, 1880.

4. Chaslin: Note sur l'anatomie pathologique de l'épilepsie essentielle: La sclérose névroglique, Compt. rend. Soc. biol. **1**:169-171, 1889.

5. Bratz, E.: Ammonshornbefunde der Epileptischen, Arch. Psychiat. **31**:820-836, 1899; Über das Ammonshorn bein Epileptischen und Paralytikern, Allg. Ztschr. Psychiat. **56**:841-844, 1899.

Kershman,[6] MacLean,[7] Lennox [8]). Nevertheless, so far as we are aware, no special investigation of this subject has yet been undertaken. It is for this reason that we have attempted to correlate the neuropathologic and the clinical data in a group of epileptic patients, focusing our attention on their psychomotor seizures or ictal psychic phenomena.

MATERIAL AND METHODS

The clinical records and the brains of 50 institutionalized epileptic patients[9] sent to the neuropathology laboratory of the Langley Porter Clinic during the period between 1946 and 1952 were examined. Particular attention was given to electroencephalograms when available. The pathologic studies were based on sections obtained from representative areas of the brain and stained according to the methods of Nissl, Holzer, and Weil, in addition to hematoxylin-eosin preparations. Special emphasis was placed on investigation of the anterior tip of the temporal lobe; the hippocampal formation, including the hippocampal gyri; the uncus; the amygdaloid nuclei; the mamillary body with the neighboring diencephalic structures; the cingulate gyrus; the corpus callosum, and the fornix.

RESULTS

Of the 50 cases, sclerosis of the cornu ammonis was present in 29 (58%). These were classified as follows: Group A: little significant change in the brain other than sclerosis of the cornu ammonis, 9 cases. Group B: scars in the temporal lobes or in both temporal and frontal lobes in addition to sclerosis of the cornu ammonis, 9 cases. The lesions in most of these cases were regarded as secondary to trauma sustained during the convulsions, except in two cases in which there was a history of trauma prior to the onset of convulsive seizures. Group C: congenitally malformed brains and severe mental deficiency, 11 cases. The last group was eliminated from consideration of clinical symptomatology as it related to sclerosis of the cornu ammonis because of the general disturbance in function of the brain.

Clinical Features.—The psychic manifestations of Groups A and B, comprising 18 cases, are listed in Table 1.

It may be seen from Table 1 that paroxysmal or ictal psychic phenomena, consisting chiefly of episodes of confusion and/or rage, occurred in 16 of the 18 cases. Such attacks might well be designated by the age-old term "epileptic mania." They were usually described in the clinical charts as follows: The patient would suddenly become confused without apparent cause, become hyperactive and violent, often blindly attacking family members, attendants, or other patients, or destroy objects about him. Such a patient could not be reasoned with, often requiring seclusion, and calmed down only after a certain time. Sometimes this episode preceded a generalized convulsion or directly followed it, in the form of postictal confusion. In some cases it was recorded that the patient showed amnesia for the events occurring during the attack, while in other cases such a description was lacking. In some instances there were short periods of confusion which were difficult to classify.

6. Jasper, H., and Kershman, J.: Electroencephalographic Classification of the Epilepsies, Arch. Neurol. & Psychiat. **45**:903-943, 1941.

7. MacLean, P. D.: Psychosomatic Disease and "Visceral Brain": Recent Developments Bearing on the Papez Theory of Emotion, Psychosom. Med. **11**:338-353, 1949.

8. Lennox, W. G.: Phenomena and Correlates of Psychomotor Triad, Neurology **1**:357-371, 1951.

9. The material was derived largely from Sonoma State Home and the Pacific Colony.

Masticatory movements were not observed in any of the cases, but these abnormalities may have been overlooked by observers of the attacks. It was noteworthy that psychotic symptoms were noted in some of the cases and that emotional changes were common in the majority. In all the cases in this series the patients had had convulsive seizures before they exhibited the psychic symptoms, the interval being more than four years in about three-fourths of the cases.

TABLE 1.—*Psychic Phenomena in Eighteen Cases of Sclerosis of the Cornu Ammonis*

Symptoms	No. of Cases		
	Total	Group A	Group B
I. Ictal psychic phenomena	16	9	7 *
(*a*) Episodes of confusion associated with rage	14	8	6
With amnesia	8	5	3
Without any record of amnesia	6	3	3
(*b*) Short periods of confusion only	2	1	1
II. Postictal confusion	10	4	6
(*a*) With rage episodes	8	4	4
(*b*) Postictal confusion only	2	0	2
III. Persistent psychotic manifestations	4	1	3
Visual and/or auditory hallucinations; religious and grandiose delusions			
IV. Emotional changes between attacks	13	7	6
Instability; irritability; impulsiveness; negativism; violence; depression			

* Group A was without any other cerebral lesions; Group B had temporal or frontotemporal posttraumatic scars in addition to sclerosis of the cornu ammonis.

TABLE 2.—*Psychic Phenomena in Fourteen Cases Without Sclerosis of the Cornu Ammonis*

Symptoms	No. of Cases	
	Total	Group B′
I. Ictal psychic phenomena	3	3 *
(1) Episodes of confusion and rage	1	1
(2) Uncinate fits	1	1
(3) Dreamy states	1	1
II. Postictal confusion	1	1
III. Persistent psychotic manifestations (delusions and hallucinations)	3	3
IV. Emotional changes between attacks (irritability, excitability, assaultiveness)	3	3

* Group B′ had lesions in the temporal or frontotemporal areas of traumatic or other etiology.

In 21 cases (42%) there was no sclerosis of the cornu ammonis. These cases were also divided into three groups: Group *A′*: no significant cerebral pathology, five cases. Group B′: temporal or frontotemporal lesions, nine cases. In the majority of these cases the lesions were of traumatic origin, incidental to the convulsive seizures, with the following exceptions: a patient with uncinate fits, in whom an old arteriosclerotic infarct was found in the right posterior temporal region, in addition to traumatic scars in the uncinate-amygdaloid area, and a patient with dreamy states, as well as automatism, in whom an old organized abscess was observed in the left posterior temporal region. Group C′: malformed brains and clinically severe mental

deficiency, seven cases. These cases, like the similar group with sclerosis of the cornu ammonis, were eliminated from the clinical discussion. The psychic symptoms in Groups A′ and B′ are listed in Table 2.

It will be noted in Table 2 that ictal psychic phenomena and/or emotional changes were far less common in this series than in that presented in Table 1. Moreover, such symptoms when present were observed only in Group B′, i. e., in cases with lesions in the temporal lobes. It was noteworthy that in five cases of this series the patients were described as well behaved, an observation which was never encountered in the group with sclerosis of the cornu ammonis.

In practically all the cases in both groups there was some degree of mental deterioration, which apparently developed as a result of repeated convulsions. There was no remarkable difference between the two groups with regard to the age of onset, the duration and frequency of convulsive seizures, or the age and cause of

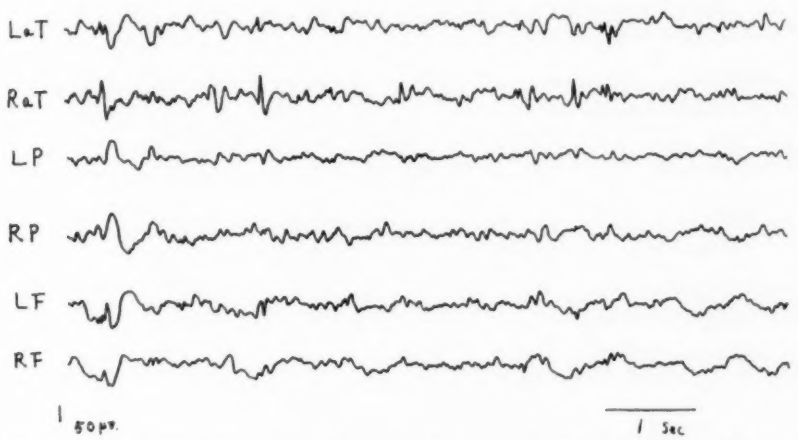

Fig. 1 (Case 2753).—Electroencephalogram (sleep record), showing spike activity in the right anterior temporal region and flattening in the left parietal region.

death. The patients with malformed brains usually had convulsive seizures very early in life, frequently before the age of 2 years. About 40% of the patients, whether in the sclerosis or in the nonsclerosis group, died of severe convulsions or of status epilepticus.

Electroencephalographic Findings.—Electroencephalograms were available in five cases with sclerosis of the cornu ammonis. Two of these cases (2753 and 2079) belonged to Group A.

Case 1.—A white man aged 53 had a history of seizures since the age of 23. These were at first grand mal attacks. Later there developed episodes of confusion and automatic behavior followed by amnesia, during which the patient often became violent and combative. Toward the end, there occurred focal seizures involving the right side of the face, followed by motor aphasia. The electroencephalogram (Fig. 1) showed spike activity in the right anterior temporal region and flattening in the left parietal region. These changes might have been related, respectively, to sclerosis of the cornu ammonis on the right and to traumatic scars in the posterior inferior frontal region on the left.

Case 2.—A white man aged 32 had a history of convulsions since the age of 14, consisting of grand mal attacks and short periods of confusion. Since the age of 29 he had exhibited increasing mental confusion and persistent hypomanic reactions. An electroencephalogram (Fig. 2 *A* and *B*) revealed diffuse slow waves, with sharp waves most prominent in the left temporal region, both in the monopolar (*A*) and in the bipolar (*B*) leads. The only lesion in the brain was sclerosis of the cornu ammonis on the left side.

Other Cases.—The three other cases belonged to Group B. In the first of these (Case 3056) nonlocalizable, 2 to 6 cps, generalized slow waves and random spikes appeared in several leads. In the second (Case 3021) there was a generalized dysrhythmia with 3 to 7 cps, slow wave

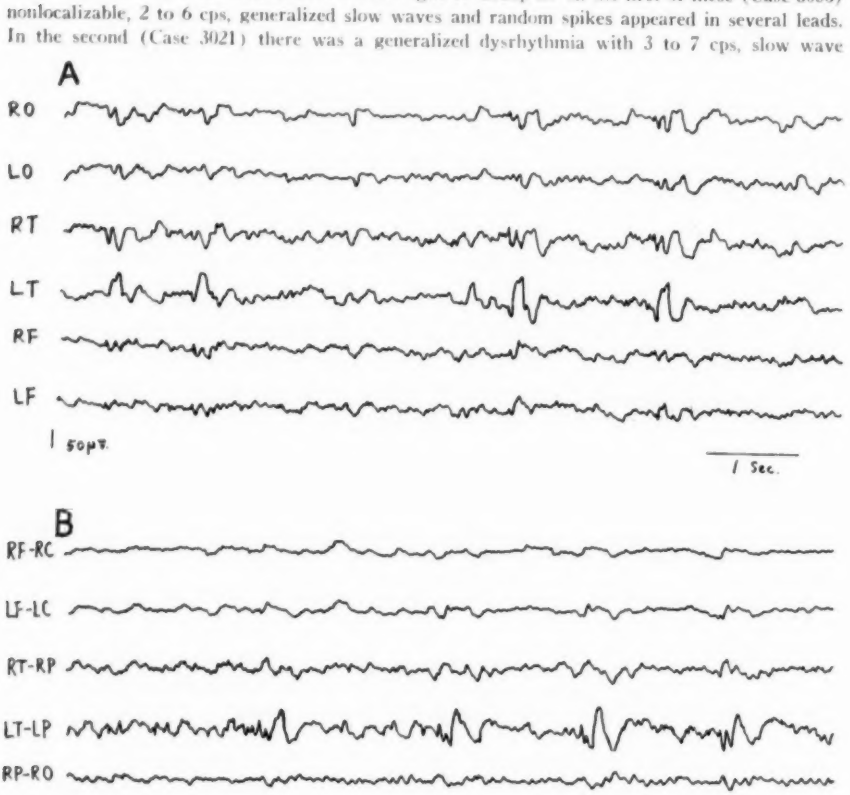

Fig. 2 (Case 2079).—Electroencephalogram, showing diffuse slow waves and sharp waves, most prominent in the left temporal (anterior temporal) region in (*A*) monopolar and (*B*) bipolar leads.

activity, the amplitude being twice as high over the right cerebral hemisphere as over the left. The right hemisphere contained scars in the temporal, frontal, and occipital regions, as well as sclerosis of the cornu ammonis. In the third (Case 3416) the electroencephalogram, taken at the age of 55, showed a left temporal focus and diffuse slow waves. One year later the electroencephalogram exhibited diffuse slow waves and "single-spike seizure discharges" oftener on the right side, especially in the anterior temporal and temporal areas. Examination of the brain in this case revealed sclerosis of the cornu ammonis on the left side, moderate gliosis of the

Fig. 3 (Case 3416).—Cornu ammonis, showing (*A*) loss of pyramidal cells (Nissl stain), (*B*) gliosis (Holzer stain), and (*C*) demyelination (Weil stain), most pronounced in Sommer's sector (h_1) and end-plate (h_5).

end-plate on the right side, and old traumatic contusions of the cortex in the midportion of the right middle and inferior temporal gyri. Electroencephalograms were also available in three cases without sclerosis of the cornu ammonis. In the first, belonging to Group A', the electroencephalogram was normal. In the second, with contusions in the posterior temporal region (Group B') a specific electroencephalographic focus was present in that area, while in the third case, with a malformed brain, there was generalized dysrhythmia.

Pathologic Features.—The pathology of sclerosis of the cornu ammonis is too well known, after the accurate descriptions of Bratz,[5] Spielmeyer,[10] and others, to require detailed description here. The histologic pictures were essentially similar in all cases, with only minor variations (Fig. 3, *A*, *B*, and *C*). Following Rose's [11] cell divisions of the hippocampus (Fig. 4), we plotted the relative intensities of the changes in different areas in Figure 5 *I* and *II*. These were determined from the appearance of the lesions in the middle third of the hippocampus ($h_1 - FD$), the

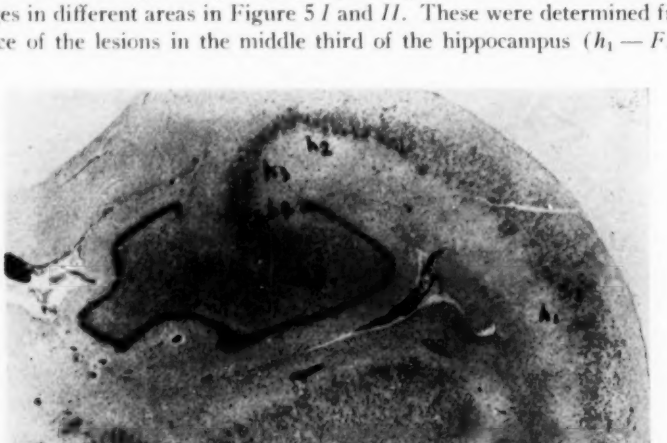

Fig. 4 (Case 2079).—Cornu ammonis (from normal [right] side), showing normal cytoarchitecture, in accord with the cell divisions outlined by Rose. Nissl stain.

amygdaloid complex (*AMG*) and the uncal cortex (*U*), and the anterior temporal tip (*AT*). The letters at the bottom of the graphs in Figure 5 are abbreviations for the traditional terms used by Spielmeyer's school,[12] i. e., Sommer's sector (*S.S.* is h_1), the dorsal resistant portion (*R* is h_2), the end-plate stem (*Es.* is h_3 and h_4), and the end-plate (*Eb* is h_5).

It can be seen that in Groups A and B (Fig. 5 *I*) seven brains showed predominantly left-sided changes of the cornu ammonis; eight brains, right-sided changes, and three brains, bilateral changes. A slight increase in glia, indicated by

10. Spielmeyer, W.: Zur Pathogenese örtlich elektiver Gehirnveränderungen, Ztschr. Neurol. u. Psychiat. **99**:756-776, 1925.

11. Rose, M.: Der Allocortex beim Tier und Mensch, J. Psychol. u. Neurol. **34**:1-111; Der Allocortex beim Tier und Mensch: Die sogenannten Reichrinde beim Menschen und beim Affen, ibid. 261-401, 1927.

12. Bodechtel, G.: Die Topik der Ammonshornschädigung, Ztschr. Neurol. u. Psychiat. **123**:485-535, 1930.

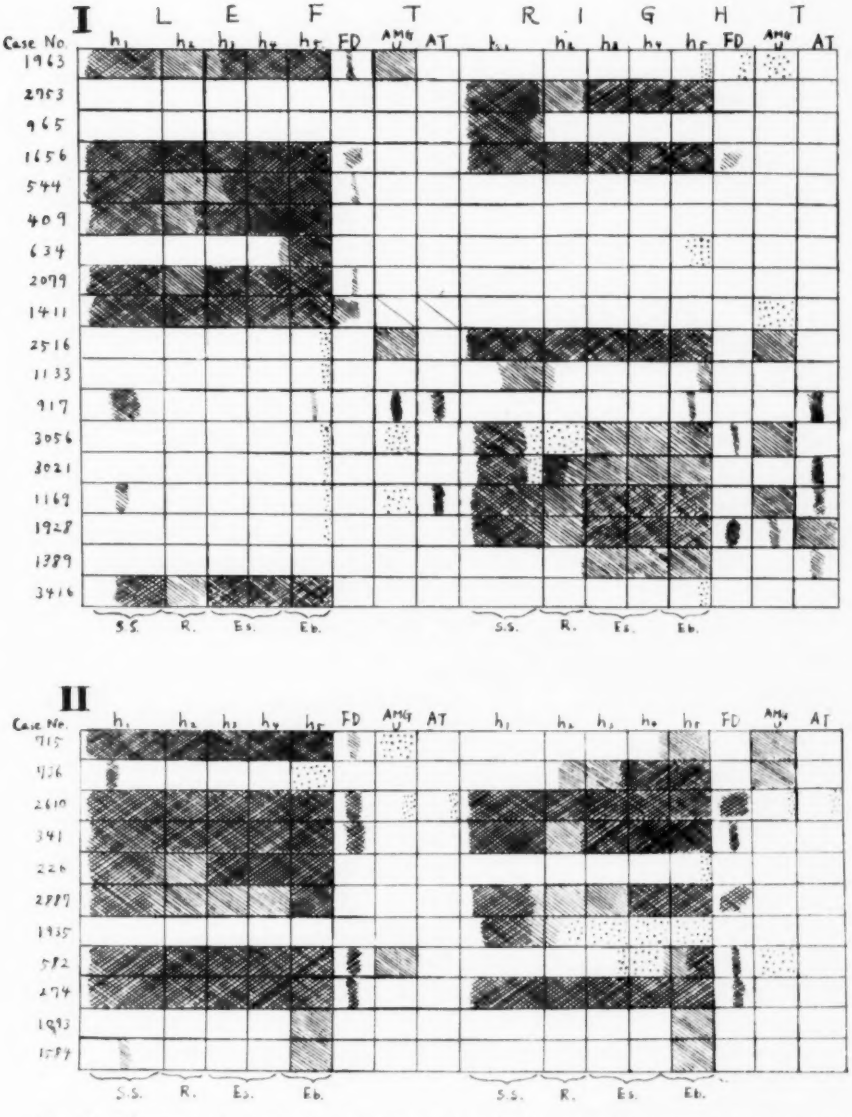

Fig. 5.—Diagrams of distribution of pathologic changes in the hippocampus and adjacent areas *I:* Groups *A* and *B*; *II:* Group *C*. Here, h_1 to h_5 indicate hippocampus; *FD*, fascia dentata; *AMG*, amygdaloid nuclei; *U*, uncal cortex; *AT*, anterior part of temporal lobe. For explanation of *S.S.* to *Eb*, see text. Cross hatching represents severe gliosis; hatching, moderate, and dots, mild gliosis.

dots, is not counted in the over-all picture. In Group C (Fig. 5*H*), nine brains showed bilateral changes in the cornu ammonis, and one brain each left-sided and right-sided changes. It can be concluded, therefore, that in cases of epilepsy with malformed brains, sclerosis of the cornu ammonis, when it exists, tends to be bilateral. This fact has already been noted by Bratz.[13] On the other hand, in "idiopathic" epilepsy, sclerosis of the cornu ammonis is usually unilateral, the difference of incidence on the left and on the right side being very slight.

The only other noteworthy pathologic finding was a diffuse dropping-out of the Purkinje cells of the cerebellum in about two-thirds of the cases of either group.

COMMENT

Pathogenesis of Sclerosis of the Cornu Ammonis.—Bratz [5] considered sclerosis of the cornu ammonis a congenital lesion. The Vogts [14] regarded it as strong evidence for their theory of *Pathoklise,* arguing that the sharp differences in cell morphology in Sommer's sector, the end-plate, the portion between them, and the subiculum represented differences in physicochemical structure. According to Spielmeyer and his associates,[15] the change was explained on a vascular basis. They demonstrated ischemic changes in Sommer's sector and in the end-plate in acute cases of epilepsy and assumed that in chronic cases the degenerated ganglion cells were ultimately replaced by glia, to produce the final picture of sclerosis. Moreover, they observed similar changes in primary vascular or circulatory disorders. In the absence of vascular disease in "idiopathic" epilepsy, they advanced the theory of angiospasm.

It is known that the anteroinferior portion of the hippocampal formation is supplied by the anterior choroidal artery, while its major part is supplied by the posterior cerebral artery. The branches of these two arteries anastomose near the anterior end of the hippocampal formation. According to Uchimura,[16] Sommer's sector, unlike the other portions, is supplied by only one artery, which he named *Sektorgefäss.* Originating in the above-mentioned branches, this vessel pierces the surface of the dentate fascia and runs in the septum between it and the hippocampus, assuming a relatively long and twisted course to reach Sommer's sector, where it forms a rather poor capillary network. This vessel has few branches and, more than any other blood vessel in the brain, possesses the character of an end-artery. The capillary network in the end-plate is also relatively poor. As a result, the ganglion cells of these areas are extremely vulnerable to circulatory insufficiency. Moreover, because of its long, twisted course in the septum, where gliosis tends to occur early, this vessel is predisposed to angiospasm. Altschul [17] first noted that these *Sektorge-*

13. Bratz, E.: Das Ammonshorn bei epileptischen, paralytikern, senildementen, und anderen Hirnkranken, Monatsschr. Psychiat. u. Neurol. **47**:56-62, 1920.

14. Vogt, C., and Vogt, O.: Erkrankungen der Grosshirnrinde, im Lichte der Topistik, Pathoklise und Pathoarchitektonik, J. Psychol. u. Neurol. **28**:1-171, 1922.

15. Uchimura, I.: Zur Pathogenese der örtlich elektiven Ammonshornerkrankung, Ztschr. Neurol. u. Psychiat. **114**:567-601, 1928.

16. Uchimura, I.: Über die Gefässversorgung des Ammonshornes, Ztschr. Neurol. u. Psychiat. **112**:1-19, 1928.

17. Altschul, R.: Die Blutgefässverteilung im Ammonshorn, Ztschr. Neurol. u. Psychiat. **163**:634-642, 1938.

fässe, consisting of 12 to 15 branches, arise from the trunk in a rake-like pattern in the human brain. Scharrer [18] found the same vascular pattern in the artery supplying the cornu ammonis of the opossum, and he explained on this basis the sclerosis of the cornu ammonis which follows carbon monoxide poisoning. This observation was confirmed by Nilges,[19] who found such rake-like branching of the blood vessels to the hippocampus in many mammals, including the monkey. Alexander and Putnam [20] found that Sommer's sector, unlike other parts of the brain, was supplied by branches not larger than "vessels of the fourth order," and that they were the smallest ones among those of the same order, being 20 to 16 μ in diameter. Sugar and Gerard,[21] using the brain potential as an indicator, showed that the gray matter of the cerebellum and the cornu ammonis were the areas of the brain most liable to be affected by anemia.

But while the particular angioarchitecture of the hippocampal formation accounts for its vulnerability, there is no evidence of any widespread vasoconstriction occurring during or immediately preceding a seizure. The studies by Gibbs and associates [22] and Penfield and associates [23] showed, rather, an increase of cerebral blood flow during a seizure. The latter authors maintained that such increased circulation occurs in the area of cortex which is involved in the discharge producing the seizure and that it is secondary to that discharge. Other areas of the cortex may show no alteration in circulation, although in some instances there may be decreased circulation of short duration at a distance from the discharging zone. There are two possible explanations for these discrepancies: 1. The ganglion cells of the cornu ammonis are involved in the discharge and are damaged, owing to relative ischemia; i. e., the circulation to that area is insufficient to supply the demand made by the cells, which are working excessively, although the absolute blood flow increases. 2. The cornu ammonis is not involved in the discharge and is damaged because the blood supply to the discharging regions increases, thereby causing a relative decrease in blood flow to the hippocampus.

Why some epileptics show sclerosis of the cornu ammonis and others do not, and why many patients with "idiopathic" epilepsy show unilateral changes and most of those with malformed brains show bilateral changes, is not clear. Those with malformed brains usually have severe convulsive seizures, dating from infancy. Although the infant's brain is more resistant to anoxia and hypoglycemia, many clinical facts suggest that it is rather less resistant to violent seizure activity than is the adult brain. Thus, the bilateral change could easily occur, particularly since all parts of the cerebral cortex must be involved in the discharge when the brain

18. Scharrer, E.: Vascularization and Vulnerability of the Cornu Ammonis in the Opossum, Arch. Neurol. & Psychiat. **44**:483-506, 1940.

19. Nilges, R. G.: Arteries of the Mammalian Cornu Ammonis, J. Comp. Neurol. **80**:177-190, 1944.

20. Alexander, L., and Putnam, T. J.: Pathological Alterations of Cerebral Vascular Patterns, A. Res. Nerv. & Ment. Dis., Proc. **18**:471-543, 1938.

21. Sugar, O., and Gerard, R. W.: Anoxia and Brain Potentials, J. Neurophysiol. **1**:558-572, 1938.

22. Gibbs, F. A.; Lennox, W. G., and Gibbs, E. L.: Cerebral Blood Flow Preceding and Accompanying Epileptic Seizures in Man, Arch. Neurol. & Psychiat. **32**:257-272, 1934.

23. Penfield, W.; von Santha, K., and Cipriani, A.: Cerebral Blood Flow During Induced Epileptiform Seizures in Animals and Man, J. Neurophysiol. **2**:257-267, 1939.

is malformed. For the unilaterality of sclerosis of the cornu ammonis seen in many cases of idiopathic epilepsy there seems to be no convincing explanation. The reason given by Bratz [5] for unilateral seizures with sclerosis of the cornu ammonis in the discharging hemisphere is that in some cases the hippocampus may be involved in the seizure discharge on one side only. In two cases of post-traumatic epilepsy (Cases 2516 and 1133) in our series, sclerosis of the cornu ammonis was observed on the same side as the traumatic lesion.

Functional Anatomy of the Hippocampal Formation and Related Structures.—There has been much speculation about the functions of the hippocampal formation. For many years this area was regarded by various authors as a part of the rhinencephalon, i. e., an association center for olfaction. Rose,[11] however, concluded that the hippocampus must have a nonolfactory function, since many microsmatic or anosmatic mammals have a well-developed and differentiated cornu ammonis. Brodal [24] found no support for the concept that the hippocampus has any important relation to the sense of smell. Penfield and Erickson [25] believed the hippocampus to be a focus for olfactory seizures, but on stimulation they did not produce such responses. Ariëns Kappers, Huber, and Crosby [26] stated that the hippocampal cortex serves as a correlation center for olfactory, visceral, and somatic impulses. Papez,[27] in 1937, proposed that the hypothalamus, the anterior thalamic nuclei, the gyrus cinguli, the hippocampus, and their interconnections constituted a harmonious mechanism for elaboration of emotions and emotional expression. According to him, this central emotive process may be built up in the hippocampal formation and transferred to the mamillary body, and thence through the anterior thalamic nuclei to the cortex of the cingulate gyrus. Radiation of the emotive process from the latter to other regions of the cerebral cortex would add emotional coloring to psychic processes occurring elsewhere. This theory has recently been elaborated upon further by MacLean.[7] Klüver and Bucy,[28] after removing both temporal lobes, including the uncus, the amygdaloid nuclei, and the greater part of the hippocampus in a series of monkeys, noted "psychic blindness," oral tendencies, "hypermetamorphosis," absence of emotional reactions, and, less constantly, increase in sexual activity. These changes did not appear when the removal was limited to the cortex and the hippocampus was left intact; neither did they appear after unilateral removal, although in that case there was a change in the direction of greater tameness. However, none of Allen's [29] dogs with ablation of the hippocampus showed such symptoms, and neither elementary nor conditioned olfactory reflexes were influenced.

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24. Brodal, A.: The Hippocampus and the Sense of Smell: Review, Brain **70**:179-222, 1947.

25. Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization, Springfield, Ill., Charles C Thomas, Publisher, 1941.

26. Ariëns Kappers, C. U.; Huber, G. C., and Crosby, E. C.: The Comparative Anatomy of the Nervous System of Vertebrates, Including Man, New York, The Macmillan Company, 1936, Vol. 2.

27. Papez, J. W.: A Proposed Mechanism of Emotion, Arch. Neurol. & Psychiat. **38**:725-743, 1937.

28. Klüver, H., and Bucy, P. C.: Preliminary Analysis of Functions of the Temporal Lobes in Monkeys, Arch. Neurol. & Psychiat. **42**:979-1000, 1939.

29. Allen, W. F.: Effect of Ablating the Frontal Lobes, Hippocampi, and Occipito-Parieto-Temporal (Excepting Pyriform Areas) Lobes on Positive and Negative Olfactory Conditioned Reflexes, Am. J. Physiol. **128**:754-771, 1940.

Anatomically, there are no, or very few, direct olfactory fibers to the hippocampus. According to Lorente de Nó,[30] there are three major afferent systems to the hippocampus: (1) fibers from the supracallosal striae to the uppermost portion of the hippocampus; (2) fibers entering through the cingulum to the middle portion of the hippocampus, and (3) fibers from the entorhinal area to the lowermost, or major, portion of the hippocampus. The fornix is the main efferent pathway, arising from the pyramidal cells of the hippocampus and the polymorphic layer of the dentate gyrus (Allen[31]). These efferent fibers terminate mainly in the mamillary body, the perifornical nucleus, and the septal region. On the basis of electrical and strychnine neuronography, several authors[32] have recently concluded that at least a part of the hippocampus and adjacent areas have close two-way connections with the temporal tip. This concept finds confirmation in our cases of sclerosis of the cornu ammonis in which the electroencephalograms showed the most prominent spike or wave foci in the anterior temporal regions.

Ictal Psychic Phenomena.—Hughlings Jackson,[33] in 1875, referred to "temporary mental disorders after epileptic paroxysms" as states of mental automatism. He believed that the automatism was always postepileptic and was due to loss of control from the highest centers, which had been paralyzed by the epileptic discharge. He admitted, however, that there are cases in which the automatism is not preceded by a convulsion. This state was later called by Penfield and Erickson[25] "ictal automatism," implying that the highest level could be paralyzed by a discharge during seizure. This is thought to be identical with a type of epilepsy designated by Gibbs, Gibbs, and Lennox[34] in 1937 as "psychomotor," as a clinical and electroencephalographic entity. Jackson also made a detailed description of a variety of epilepsy which he termed "dreamy state," the characteristic features of which were illusions or hallucinations, sometimes followed by automatism and sometimes preceded by crude sensations of smell ("uncinate fits"). Later, Penfield and Erickson,[25] on the basis of operative findings, asserted that the focus of dreamy-state seizures was in the temporal lobe. Jasper concluded from electroencephalographic evidence that automatisms also originated in the temporal lobe. Gibbs and associates,[35] in 1948, using sleep technique, localized the electroencephalographic focus for psychomotor epilepsy in the anterior tip of the temporal lobe in the great majority of cases.

These two types of epilepsy, which are intimately connected with each other, are nowadays called "temporal lobe seizures" or "temporal epilepsy." In our series it

30. Lorente de Nó, R.: Studies on the Structure of the Cerebral Cortex: The Area Entorhinalis, J. Psychol. u. Neurol. **45**:381-438, 1933; Continuation of Study of Ammonic System, ibid. **46**:113-177, 1934.

31. Allen, W. F.: Degeneration in the Dog's Mammillary Body and Ammon's Horn Following Transection of the Fornix, J. Comp. Neurol. **80**:283-291, 1944.

32. Pribram, K. H.; Lennox, M. A., and Dunsmore, R. H.: Some Connections of the Orbito-Fronto-Temporal, Limbic and Hippocampal Areas of Macaca Mulatta, J. Neurophysiol. **13**:127-135, 1950. Ajmone-Marsan, C., and Stoll, J. Jr.: Subcortical Connections of the Temporal Pole in Relation to Temporal Lobe Seizures, A. M. A. Arch. Neurol. & Psychiat. **66**:669-686, 1951.

33. Jackson, J. H.: Selected Writings of John Hughlings Jackson, edited by J. Taylor, London, Hodder & Stoughton, Ltd., 1931, Vol. 1.

34. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Epilepsy: A Paroxysmal Cerebral Dysrhythmia, Brain **60**:377-388, 1937.

35. Gibbs, E. L.; Gibbs, F. A., and Fuster, B.: Psychomotor Epilepsy, Arch. Neurol. & Psychiat. **60**:331-339, 1948.

was clear that the patients showing ictal psychic phenomena had had lesions either in the hippocampal formation or in the temporal cortex, or in both, although the reverse was not always true. Many of these patients, especially those with amnesia for events during the episodes, can be considered to have had true psychomotor epilepsy. It is noteworthy that none of our patients with sclerosis of the cornu ammonis exhibited dreamy states; rather, they showed a rage component. It may be suggested that such elaborate psychic phenomena as the dreamy state are concerned with the cortex of the temporal lobe or the temporal cortex-pulvinar circuit, while the rage component is possibly due to bombardment of the hypothalamus by a hippocampal focus.

It has been observed that if there is a scar in the epileptic brain, either primary, such as one due to trauma, or secondary, due to the seizure itself, epileptogenic foci may develop around it in the course of time. Since sclerosis of the cornu ammonis represents a distinct scar, one can expect in the epileptic brain discharging foci in neighboring structures, most likely in the presubiculum and adjacent parts of Sommer's sector. These parts are known to send fibers both to the temporal lobe, possibly the tip, and to the hypothalamus, through the fornix. Thus, a focus in these areas could fire the temporal tip to produce a secondary focus there, with spike activity manifested in the anterior temporal region, and it could also bombard the hypothalamus. Since the main endings of the fornix fibers are in the mamillary body, the perifornical nucleus, and the septal region, specific symptoms can be expected to develop from bombardment of these regions. According to Hess,[36] chewing-licking movements are elicited chiefly by stimulation of the septal region, and rage responses are observed on stimulation of the perifornical nucleus and adjacent areas. Therefore, these two phenomena are oftenest associated with the automatism. Although the masticatory movements were not noted in the charts, the rage component was a prominent feature in our cases with sclerosis of the cornu ammonis. This is also an important symptom in a form of epilepsy characterized by 14 and 6 cps positive spikes, which, according to Gibbs and Gibbs,[37] is of thalamic or hypothalamic origin. Most of the patients in our series had convulsive seizures preceding the development of ictal psychic phenomena. According to Lennox,[8] 63% of patients with psychomotor attacks have a history of convulsions. There may be two types of temporal lobe epilepsy, primary and secondary. The former is due to trauma, tumor, vascular lesions, or other lesions directly involving the temporal lobe. Our cases of dreamy-state seizures and uncinate fits were of this type. The latter type develops as a result of convulsions; i. e., the patient, in the course of repeated convulsions, acquires scars in the cortex or in the cornu ammonis, which, in turn, become foci for temporal lobe seizures. Most of our cases belonged to the latter category.

In not all cases of psychomotor epilepsy with spike foci in the anterior temporal region have pathologic changes been found in the cortex of the temporal lobe removed during operation. Thus, in more than one-half of 25 cases reported by Bailey and

36. Hess, W. R.: Das Zwischenhirn: Syndrome, Lokalisationen Funktionen, Basel, Benno Schwabe & Co., 1949.

37. Gibbs, E. L., and Gibbs, F. A.: Electroencephalographic Evidence of Thalamic and Hypothalamic Epilepsy, Neurology **1**:136-144, 1951.

Gibbs,[38] and in 9 of 23 cases reported by Green and associates,[39] examination failed to show pathology in the cortex of the temporal lobe. In such cases, Green and associates noted that rage, which was a feature of the attacks or of the interseizure psychiatric abnormalities, tended to recur after operation. It may be suggested that sclerosis of the cornu ammonis existed in these cases and that the focus around the scar produced the secondary spike foci in the anterior temporal cortex, the removal of which could not be expected to abolish the psychomotor seizures.

Belinson [40] reported a higher incidence of the psychomotor type of electroencephalographic pattern in institutionalized epileptics (26%) than in noninstitutionalized epileptics (10%). It is obvious that such epileptics are institutionalized because of their behavior abnormalities. A recent report by Lennox [5] indicated that 20.7% of patients with epilepsy had a history of psychomotor seizures. On this basis, the calculated incidence of institutionalized epileptics having psychomotor seizures would be 54% (20.7×2.6), which is close to the incidence (59%) in the patients with ictal psychic phenomena in our series.

SUMMARY

The brains of 50 institutionalized epileptic patients were examined and their clinical records reviewed, with special emphasis on the presence or absence of ictal "psychic phenomena." The results are summarized, as follows:

1. In 29 cases there was sclerosis of the cornu ammonis. These cases were classified as follows: Group A, sclerosis of the cornu ammonis without other remarkable changes, 9 cases; Group B, frontal or frontotemporal traumatic lesions, in addition to the sclerosis of the cornu ammonis, 9 cases; Group C, congenitally malformed brains, 11 cases. Sclerosis of the cornu ammonis was unilateral in Groups A and B and bilateral in Group C. In nine cases of Group A and in seven cases of Group B ictal psychic phenomena were exhibited, a prominent feature of which was rage. The incidence of emotional changes between attacks was high in these groups. The cases of malformed brains were not considered in the clinical evaluation because of the severe mental deficiency.

2. In 21 cases there was no sclerosis of the cornu ammonis. These were subdivided as follows: Group A′, no cerebral changes, five cases; Group B′, temporal or frontotemporal traumatic lesions, nine cases, and Group C′, malformed brains, seven cases. Ictal psychic phenomena and emotional changes were not observed in Group A′ and were seen in only three cases of Group B′. The phenomenon of rage was observed in only one of the latter cases.

3. The electroencephalograms, obtained in a few of the cases showed a spike or sharp-wave focus predominantly in the anterior temporal region on the side of sclerosis of the cornu ammonis.

The possible role of the hippocampal formation in psychomotor epilepsy or temporal-lobe automatism is discussed.

38. Bailey, P., and Gibbs, F. A.: Surgical Treatment of Psychomotor Epilepsy, J. A. M. A. **145**:365-370, 1951.

39. Green, J. R.; Duisberg, R. E. H., and McGrath, W. B.: Focal Epilepsy of Psychomotor Type: A Preliminary Report of Observations on Effects of Surgical Therapy, J. Neurosurg. **8**:157-172, 1951.

40. Belinson, L.: Electroencephalographic Characteristics of Institutionalized Epileptics, Am. J. Ment. Deficiency **52**:9-15, 1947.

AGONAL NATURE OF THE CEREBRAL RING HEMORRHAGES

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CEREBRAL ring hemorrhages are seen in a variety of diseases, such as fat embolism, laceration of the brain, acute Plasmodium falciparum malaria, postvaccinial and parainfectious encephalitides, pernicious anemia, aplastic anemia and leukemia, and intoxications (barbiturates, neoarsphenamine, arsphenamine), as reviewed by Kirschbaum,[1] Dietrich,[2] Weimann,[3] Lindau,[4] Dürck,[5] Wolff,[6] Winblad,[7] Sjövall,[8] and others. These hemorrhages may occur in such large numbers throughout the white matter that the hemorrhagic tendency is considered one of the important features of the disease process. This justifies the use of the term brain purpura (Schmidt[9]), acute hemorrhagic leucoencephalitis (Alexander and Putnam,[10] Hurst,[11] Henson and Russell[12]), and acute necrotizing hemorrhagic encephalopathy (Adams, Cammermeyer, and Denny-Brown[13]). The effusions of blood are thought to take place in diseases in which the nerves to the vessels have been paralyzed and stasis has thereby been furthered, with diapedesis hemorrhages,

1. Kirschbaum, M. A.: Über kapillare Gehirnblutungen, Frankfurt. Ztschr. Path. **23**:447-470, 1920.

2. Dietrich, A.: Die Entstehung der Ringblutungen des Gehirns, Ztschr. ges. Neurol. u. Psychiat. **68**:351-368, 1921.

3. Weimann, K.: Über Hirnpurpura bei akuten Vergiftungen, Deutsche Ztschr. ges. gerichtl. Med. **1**:543-561, 1922; Intoxikationen, in Spielmeyer, W.: Die Anatomie der Psychosen, in Bumke, O.: Handbuch der Neurologie und Psychiatrie, Berlin, Springer-Verlag, 1930.

4. Lindau, A.: Über die Natur und die Pathogenese der Einzelveränderungen bei Encephalitis haemorrhagica und Purpura cerebri, Frankfurt. Ztschr. Path. **30**:271-288, 1924.

5. Dürck, H.: Über die mit herdförmigen Gliaproduktionen einhergehenden Erkrankungen des Zentralnervensystems, Arch. Schiffs- und Tropen-Hyg. **29**:43-76, 1925.

6. Wolff, K.: Beitrag zur Morphologie der Kreislaufstörungen im Gehirn: Bau und Entstehung der Ringblutungen, Virchows Arch. path. Anat. **298**:98-160, 1936.

7. Winblad, S.: Über Purpura cerebri bei Vergiftung mit nitrosen Gasen nebst einer Studie über Morphologie und Pathogenese der kapillaren Hirnblutungen, Deutsche Ztschr. ges. gerichtl. Med. **33**:73-94, 1940.

8. Sjövall, H.: Genesis of Skull and Brain Injuries, Acta path. et microbiol. scandinav., Supp. 48, pp. 111-151, 1943.

9. Schmidt, M. B.: Über Gehirnpurpura und hämorrhagische Encephalitis, Beitr. path. Anat. u. allg. Path., Supp. 7, pp. 419-455, 1905.

10. Alexander, L., and Putnam, T. J.: Pathological Alterations of Cerebral Vascular Patterns, A. Res. Nerv. & Ment. Dis., Proc. **18**:471-543, 1938.

11. Hurst, E. W.: Acute Hemorrhagic Leuco-Encephalitis; Previously Undefined Entity, M. J. Australia **2**:1-16, 1944.

12. Henson, R. A., and Russell, D. S.: Acute Hemorrhagic Leuco-Encephalitis: Report of Case, J. Path. & Bact. **54**:227-234, 1942.

13. Adams, R. D.; Cammermeyer, J., and Denny-Brown, D.: Acute Necrotizing Hemorrhagic Encephalopathy, J. Neuropath. & Exper. Neurol. **8**:1-29, 1949.

as described by Natus [14] and Ricker.[15] The renewed evaluation of the anatomical characteristics of the cerebral ring hemorrhages has not confirmed such an assumption, and therefore a new hypothesis concerning their pathogenesis is presented in this paper.

ANATOMICAL FEATURES OF RING HEMORRHAGES

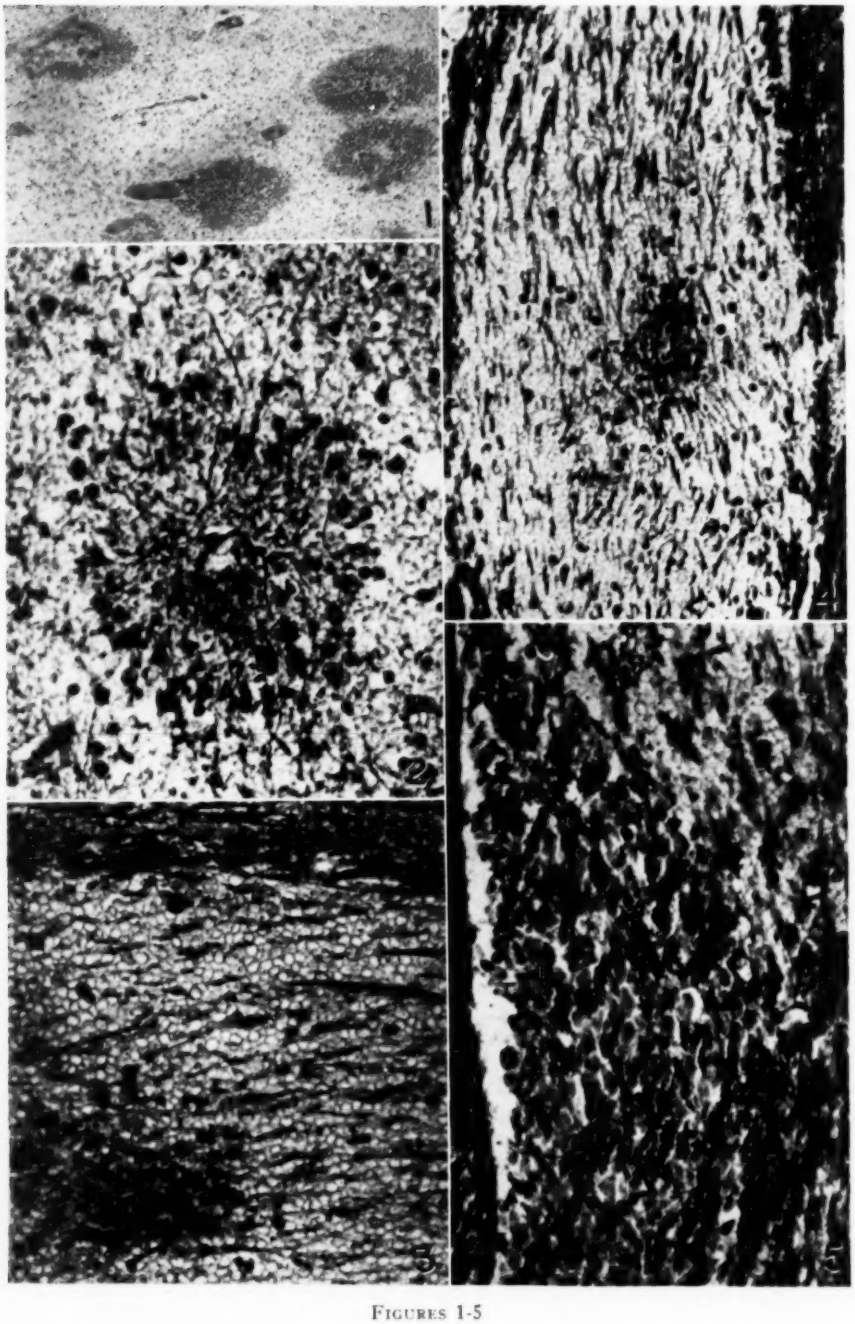
A. Typical Appearance.—The ring hemorrhages are confined to cerebral white matter, and they have a fairly characteristic structure, comprising a zone of red blood cells around a perivascular focus of necrosis (Fig. 1). In some instances the blood appears to have effused from a widely ruptured vein, as indicated in the central hemorrhage of Figure 1 and in the schematic drawings of Figures 6 and 7. The hemorrhagic zone is composed of blood cells identical with those filling the vascular system. A similar feature pertains to the hemorrhages in cases of malaria, in which the blood cells are filled with parasites and pigment. Examination of silver-impregnated and myelin-stained sections from the zone of hemorrhages reveals normal axons (Figs. 2 and 3) and intact myelin sheaths (Fig. 4). These constituents, as well as astrocytes and oligodendrocytes, are only pushed aside; degenerative changes are not demonstrated. The adjacent tissue is somewhat darker in color because of moderate compression following expansion of the hemorrhage, but no reactive changes take place.

The central focus displays changes of varying intensity. Thus, the tissue may be transformed into a homogeneous, amorphic substance or into a nodule of reactive cells. These cells are glial and mesodermal, and their appearance depends on the age of the lesion. In the focus are found fragmented axons (Figs. 2 and 3), completely disintegrated myelin sheaths, and necrosis of the glial cells. The central part of the lesion is often occupied by a vessel, which is filled with fibrin, fat embolus, or normal red blood cells; but in most instances the entire central part is transformed into an amorphic structure. The presence of fibrin in the necrotized center is revealed by the occurrence of fibers, either pink, in sections stained with hematoxylin and eosin or purplish, in sections stained with phosphotungstic acid hematoxylin. The fibrin is deposited in the thrombus, in the wall of the vessels, and in the necrotized perivascular tissue; in the last instance it forms a network of threads radiating from the vessel. The microglial cells might be a faded blue in sections stained with Prussian blue because of phagocytosis of iron. Fat-filled macrophages are also identified in older lesions.

B. Atypical Appearance.—In cases of cerebral purpura the minute hemorrhages may present a varied appearance, different from that of the ring hemorrhages. In the white matter massive rounded hemorrhages are seen next to occluded veins. These hemorrhages are probably part of ring hemorrhages in which the necrotized focus has been cut away by the microtome. Some hemorrhages are seen only partially to cover minute necrotic foci in the white matter; these are considered to

14. Natus, M.: Beiträge zur Lehre von der Stase nach Versuchen am Pankreas des lebenden Kaninchens, Virchows Arch. path. Anat. **199**:1-82, 1910.

15. Ricker, G.: Die Entstehung der pathologisch-anatomischen Befunde nach Hirnerschütterung in Abhängigkeit vom Gefässnervensystem des Hirnes, Virchows Arch. path. Anat. **226**:180-212, 1919.



FIGURES 1-5

(Legend continued on next page)

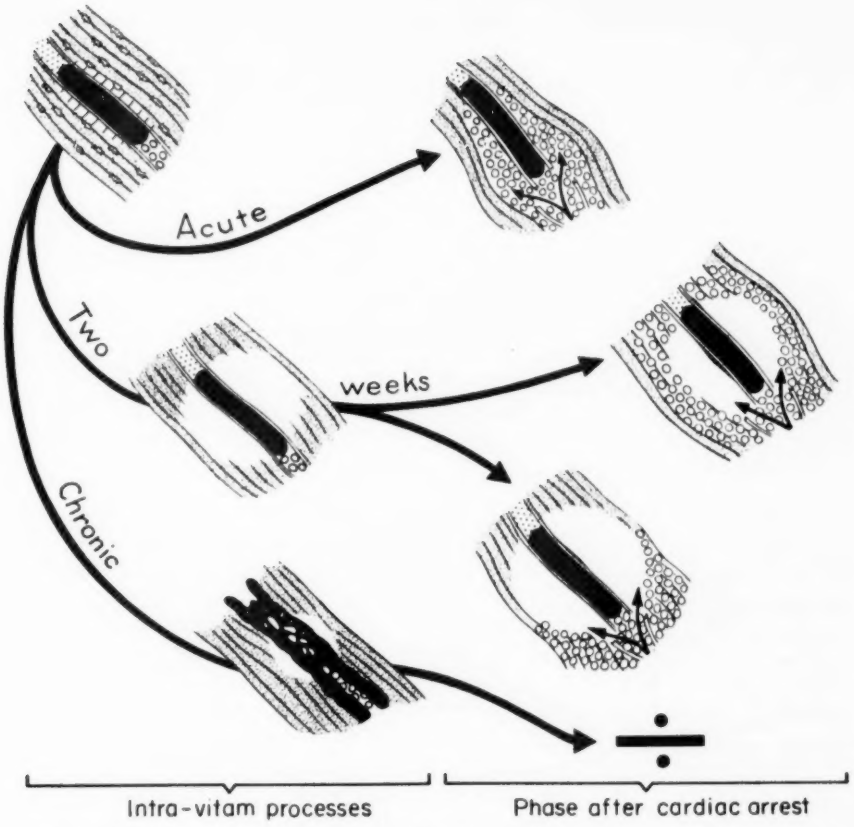


Fig. 6.—Diagram of the development of ring hemorrhages as the result of rupture of a vessel and effusion of blood at the moment of cardiac arrest. This is a passive mechanism complicating intravitam features of capillary thrombosis. The upper arrow indicates an acute phase of the tissue lesion, i. e., before a necrosis is fully developed; the blood effusion is limited to the minute area of ischemia around the vessel. The central arrows indicate the reaction when the lesion is from a few hours to two weeks old; the effusion of blood from the ruptured vessels proceeds to a ring-shaped hemorrhage or remains at one side of the necrosis. The lower arrow indicates the chronic stage; the hyperplastic wall of the vessel resists the backflow of venous blood; hence no rupture or effusion of blood. Armed Forces Institute of Pathology Negative No. 219766-18024.

EXPLANATION OF FIGURES 1-5

Fig. 1.—Ring hemorrhages in cerebral white matter, in a case of fat embolism of four days' duration. Hemorrhage is from a dilated and widely ruptured vein. Thionine; pyroxylin embedding.

Fig. 2.—Ring hemorrhage, in a case of fat embolism and coma of 46 hours' duration. The necrotic center contains swollen fragments of degenerated axons; nuclei of proliferated microglial cells form a peripheral ring. The encircling hemorrhagic zone is penetrated by delicate, intact axons. Bodian silver impregnation; paraffin embedding.

Fig. 3.—Ring hemorrhage, in a case of acute P falciparum malaria and coma of 40 hours' duration. The encircling hemorrhagic zone contains parasitized red blood cells and slender, intact axons. At the lower left is a central minute necrosis of swollen fragments of degenerated axons; in the upper part are normal axons of white matter. Bodian silver impregnation; paraffin embedding.

Fig. 4.—Ring hemorrhage, from the same case as that in *3*. The encircling hemorrhagic zone contains blood cells and scattered intact myelin sheaths, pushed apart by the blood cells. Loyez iron-hematoxylin stain; paraffin embedding.

Fig. 5.—Minute necrosis, from the same case as that in *3* and *4*, showing recent alteration, resulting in swollen axons. The hemorrhage seen at the upper right is on one side only. Loyez iron-hematoxylin stain; paraffin embedding.

be ring hemorrhages which are incomplete because the blood flow was not sufficiently strong to encircle the focus of necrosis (Figs. 5 and 6). In addition to these, the walls of the ventricles are pierced by discrete, round hemorrhages, which are limited to the perivenous space, the so-called subependymal hemorrhages. Lesions of longest duration contain minute foci of necrosis and glial reaction, whereas those of shortest duration contain similar foci encircled by the ring hemorrhage. The necrotic foci are all of the same origin. Since patients with acute falciparum malaria and cerebral fat embolism frequently succumb within a week, the brain usually contains multiple ring hemorrhages. In cases of subacute falciparum malaria, pernicious anemia, and leukemia of long duration the brain is likely to contain, besides typical ring hemorrhages, nonhemorrhagic foci of necrosis, called granulomas by Dürck [5] and *Ringwallherdchen* by Oeller,[16] Schröder,[17] and Wohlwill.[18] No traces of hemorrhages were seen in or around such "granulomatous" lesions, which are not due to a chronic infectious reaction but are identical with the scar reaction of minute infarctions.

NEW HYPOTHESIS CONCERNING FORMATION OF RING HEMORRHAGES

The hypothesis takes into consideration some of the hemodynamic properties of the normal brain (Fig. 7*A*). As the result of heart activity, the propulsive blood possesses an energy which makes it possible for the blood cells to move through the capillaries and into the veins. Within the skull any dilatation of vessels is suppressed by the tension of the tissue; moreover, any pulsation from arteries is transmitted in all directions to the venous channels. Contrary to the condition in other organs, the blood in the brain does not lose its energy in dilated vessels and soft tissues, but seems to retain most of it after reaching the veins.

At the moment of arrest of cardiac activity, the veins become engorged, particularly in the neck, with resulting increased pressure in the superior vena cava (Riml [19]; Henderson, Oughtersen, Greenberg, and Searle [20]; Ralston, Collings, Taylor, and Ogden [21]). These two factors build up an obstacle which causes regurgitation of the remaining venous blood (Fig. 7*B*). The impact of regurgitated venous blood and the sudden increase in venous pressure exert a stress on the entire venous system. In general, the tension of the tissue gives enough support to the venous walls to enable them to resist the impact of regurgitated blood. However, near the surface of the brain such support is poor, leading to ruptures of the wall (Fig. 7*C* and *D*). Because of this, a small amount of blood accumulates in the perivenous tissue.

16. Oeller, H.: Pathologisch-anatomische Studien zur Frage der Entstehung und Heilung von Hirnblutungen und über ihre Stellung zur "hämorrhagischen Encephalitis," Deutsche Ztschr. Nervenh. **47-48**:504-589, 1913.

17. Schröder, P.: Grosshirnveränderungen bei perniziöser Anämie, Monatsschr. Psychiat. u. Neurol. **35**:543-556, 1914.

18. Wohlwill, F.: Zum Kapitel der pathologisch-anatomischen Veränderungen des Gehirns und Rückenmarks bei perniciöser Anämie und verwandten Affektionen, Deutsche Ztschr. Nervenh. **68-69**:438-480, 1921.

19. Riml, O.: Über das Verhalten des Blutdruckes in der Vena cava bei plötzlichem Zirkulationsstillstande, Arch. exper. Path. u. Pharmakol. **139**:231-239, 1929.

20. Henderson, Y.; Oughterson, A. W.; Greenberg, L. A., and Searle, C. P.: Muscle Tonus, Intramuscular Pressure and Venopressor Mechanism, Am. J. Physiol. **114**:261-268, 1936.

21. Ralston, H. J.; Collings, W. D.; Taylor, A. N., and Ogden, E.: Venous Return in the Absence of Cardiac Drive, Am. J. Physiol. **145**:441-445, 1945.

Under pathological conditions changes in the supportive tension of the tissue or in the strength of the venous wall may predispose to ruptures. This predisposition is encountered in the minute necrosis following cerebral fat embolism; ring hemorrhages result from the regurgitation of venous blood, which at the level of capillary and venous occlusion breaks the wall of the vessel (Fig. 7 *E*). This view lends support to previous observations that the effusion originates in the central vessel (Schmidt [9]; Oeller [16]; Kirschbaum [1]; Dietrich [2]), or in the adjacent peripheral vessel (Gröndahl [22]) or in both (Winblad [7]; Broman [23]).

For the production of ring hemorrhages the preexisting minute necrosis is a condition *sine qua non*. The exact origin of the lesions is sometimes determined by the demonstration of a thrombus in the central capillary. In other instances microemboli are responsible for the cerebral foci of necrosis. Their frequent location in white matter may be due to the long capillary loops, which predispose to arrest of slowly moving emboli (Vance [24]; Blackwood, Dodds, and Sommerville [25]).

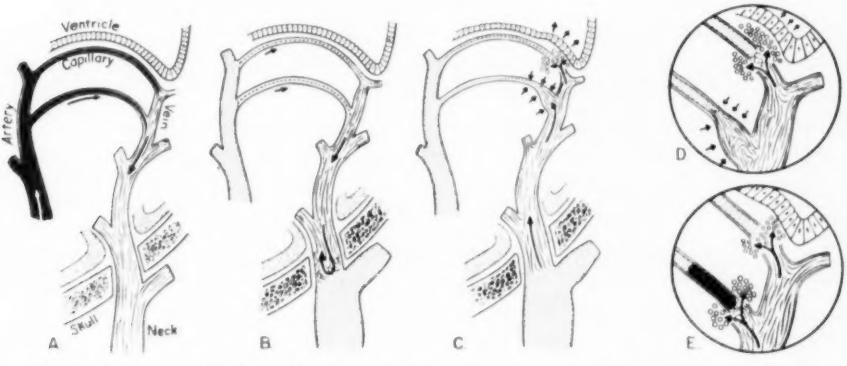


Fig. 7.—Diagram of pathogenic factors in the development of ring hemorrhages. (*A*) Normal intracranial blood flow is indicated by arrows. (*B*) At the moment of cardiac arrest the arterial blood flow is halted, whereas the flow through capillaries and veins is retained, although reduced. Conspicuous filling of the veins takes place in the neck. (*C*) The extracranial mass of blood resulting from overfilling of the large veins of the neck acts as an obstacle to the flowing intracranial blood, which therefore is regurgitated (reversed arrow). The impact of reversed blood flow increases the intravenous blood pressure, with dilatation of veins. (*D*) The tissue tension maintains an efficient pressure on the wall of the lower venule and inhibits excessive dilatation and rupture, as indicated by direction of the small arrows. If the tissue tension suddenly gives way to the increased intravenous pressure, the wall of the vein ruptures, and an effusion of blood develops around the vessel in question. (*E*) Microemboli or microthrombi predispose to rupture of the wall at the level of the occlusion, where the regurgitated venous blood meets an obstacle. At this level, also, the transition between intact and damaged wall will be a locus minoris resistentiae. From such a mechanism the ring hemorrhages are developed when the affected vessels are located in the white matter. Armed Forces Institute of Pathology Negative No. 219766-18023.

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22. Gröndahl, N. B.: Untersuchungen über Fettembolie, Deutsche Ztschr. Chir. **111**:56-124, 1911.

23. Broman, T.: Über cerebrale Zirkulationsstörungen: Tierexperimentelle Untersuchungen über Mikroembolien, Schädigungen der Gefässpermeabilität und Blutungen verschiedener Art, Acta path. et microbiol. scandinav., Supp. 42, 1940.

24. Vance, B. M.: Significance of Fat Embolism, Arch. Surg. **23**:426-465, 1931.

25. Blackwood, W.; Dodds, T. C., and Sommerville, J. C.: Atlas of Neuropathology, Edinburgh, E. & S. Livingstone, 1949.

Another important factor which may influence the formation of hemorrhage from venous rupture is the age of the lesions (Fig. 6). In the acute stage of embolism and thrombosis only the vessels are altered, whereas the tissue elements are preserved; the effusion of blood is small and perivascular (indicated in the upper part of Figure 6). From the moment of complete necrosis of tissue, the tension in the focus of necrosis increases so much that no effusion of blood takes place within it. The blood, which effuses from the ruptured vessel, is distributed around the minute necrotic focus, indicated in the middle portion of Figure 6 (compare Broman [23]). The blood cells are dispersed by the weight of pressure exerted upon them by the regurgitated blood column and by the relative pressure of necrotizing and of preserved tissues. The tendency to rupture and bleeding is diminished, and the impact of regurgitated blood does not produce effusions of blood if, because of the reactive changes, the walls of the vessels become rigid (indicated by the minus sign at the bottom of Figure 6).

COMMENT

Because of the frequent occurrence of ring hemorrhages in various diseases, these lesions have been extensively studied. Schmidt,[9] Oeller,[16] Arieti,[26] and Krücke [27] were of the opinion that the circular zones of the fully developed ring hemorrhages were obtained when the blood cells had moved from the central vessels peripherally. This view would be partly supported by the assumption that extravasated blood cells can be completely removed by the lymphatics or tissue fluid (Ricker [28]; Neubürger [29]; Schaller, Tamaki, and Newman [30]; Hultquist [31]; Weil [32]; Krücke [27]). It is difficult to believe that such a movement of red blood cells and of the red cells bearing parasites and malaria pigment could occur without leaving any traces. Moreover, the ring hemorrhages are formed around a vessel the lumen of which is completely occluded by fat, fibrin thrombus, or blood platelets, and there would scarcely be hemorrhages from a vessel empty of blood. General pathological experience would indicate that the occlusion leads to a minute perivascular tissue necrosis, which is too compact to allow any transport of blood cells. Observations on larger cerebral hemorrhages reveal that their red blood cells are removed only after degeneration of hemoglobin and phagocytosis of debris.

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26. Arieti, S.: Histopathologic Changes in Cerebral Malaria and Their Relation to Psychotic Sequels, Arch. Neurol. & Psychiat. **56**:79-104, 1946.

27. Krücke, W.: Über die Fettembolie des Gehirns nach Flugunfällen, Virchows Arch. path. Anat. u. Physiol. **315**:481-498, 1948.

28. Ricker,[15] p. 195.

29. Neubürger, K.: Arteriosklerose, in Spielmeyer, W.: Die Anatomie der Psychosen, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Springer-Verlag, 1930.

30. Schaller, W. F.; Tamaki, K., and Newman, H.: Nature and Significance of Multiple Petechial Hemorrhages Associated with Trauma of the Brain, Arch. Neurol. & Psychiat. **37**: 1048-1076, 1937.

31. Hultquist, G. T.: Über Thrombose mit Embolie der Arteria carotis und hierbei vorkommende Gehirnveränderung, Jena, Gustav Fischer, 1942.

32. Weil, A.: Textbook of Neuropathology, Ed. 2, London, William Heinemann, Ltd., 1946.

Ricker [15]; Alexander and Putnam [10]; Campbell, Alexander, and Putnam [33]; Scheinker,[34] and Marsh [35] advocated the concept of a primary generalized vascular paralysis which resulted in degenerative and hemorrhagic lesions. The sequence of pathophysiological changes was that of dilatation of vessels, leakage of plasma, diapedetic extravasation of white and red blood cells, conglutination of intravascular red blood cells, and arrest of blood flow. Thus, the diapedesis explained the production of hemorrhage and leucocytic infiltration. This mechanism of stasis was discussed as early as 1835 by Eisenmann,[36] in 1865 by Klebs,[37] and in 1883 by von Recklinghausen.[38] In the contribution by Ricker,[15] the experimental studies were confined to vessels in the omentum, liver, and pancreatic gland, i. e., to vascular systems quite different from that of the brain. Although the mechanism of stasis may account for necrosis of the central nervous tissue, no direct observations have indicated that hemorrhages develop on such basis. On morphological grounds alone, I should hesitate to accept the hemorrhages in histologic sections as indicative of stasis or diapedetic hemorrhage (Cammermeyer [39]).

Any hypothesis must explain the following characteristics of ring hemorrhages: (*a*) The minute necrosis develops independently of the encircling hemorrhage (Kirschbaum [1]; Dietrich [2]; Oesterlin [40]; Wolff [6]); (*b*) the red blood cells always appear intact (Dietrich [2]); (*c*) the demonstration of ring hemorrhages is strictly confined to histologic material; (*d*) in the living brain no similar effusions are noted (Broman [23]); (*e*) hemorrhages do not take place around chronic lesions. Accordingly, in the new hypothesis proposed here, the hemorrhages are associated with the severe hemodynamic disturbances following cardiac arrest. Despite the rupture of the walls, the hemorrhages are small because of the short time in which the blood flows after death. Since the contributing factors are fairly uniform, the size of the ring hemorrhages remains constant from case to case.

A few experimental observations may be introduced in support of the ideas presented in this paper. Meriwether and Wilson,[41] in their report of studies on the

33. Campbell, A. C. P.; Alexander, L., and Putnam, T. J.: Vascular Pattern in Various Lesions of Human Central Nervous System: Studies with Benzidine Stain, Arch. Neurol. & Psychiat. **39**:1150-1202, 1938.

34. Scheinker, I. M.: Cerebral Vascular Changes Associated with Azosulfamide and Sulfamethylthiazole Therapy, J. Neuropath. & Exper. Neurol. **2**:301-305, 1943; Vasoparalysis of the Central Nervous System, a Characteristic Vascular Syndrome: Significance in Pathology of Central Nervous System, Arch. Neurol. & Psychiat. **52**:43-56, 1944.

35. Marsh, C.: Multiple Symmetric Foci of Hemorrhagic Necrosis of Brain Due to Sulfarsphenamine Therapy: Its Occurrence in Infant Treated for Congenital Syphilis, Bull. Los Angeles Neurol. Soc. **8**:137-139, 1943.

36. Eisenmann, G.: Die vegetativen Krankheiten und die entgiftende Heilmethode, Erlangen, J. J. Palm and E. Enke, 1835, p. 308.

37. Klebs: Über die Wirkung des Kohlenoxyds auf den thierischen Organismus, Virchows Arch. path. Anat. **32**:450-517, 1865.

38. von Recklinghausen, F.: Handbuch der allgemeine Pathologie des Kreislaufs und der Ernährung, Stuttgart, F. Enke, 1883.

39. Cammermeyer, J.: The Agonal Nature of Cerebral Red Softening: Reevaluation of Morphological Findings, Acta psychiat. et neurol., to be published.

40. Oesterlin, E.: Über herdförmige Gliawucherung, Ztschr. ges. Neurol. u. Psychiat. **88**: 325-347, 1924.

41. Meriwether, L. S., and Wilson, D. C.: Cerebral Fat Embolism: Experimental Study with Special References to Reaction of Glia, Arch. Neurol. & Psychiat. **31**:338-355, 1934.

effect of fat emboli in rabbits, stated (page 349) that "a noteworthy observation was the small number of petechial hemorrhages seen." It is significant that the animals were killed by the injection of formalin, which replaced the blood. Therefore, the ring hemorrhages in these animals could not be formed. Dahl [42] found that opening of the jugular vein inhibited the production of petechial agonal hemorrhages in the wall of the ventricles. These so-called subependymal hemorrhages represent another type of minute effusion of blood following cardiac arrest. The last experiment demonstrates that by avoiding the building up of the obstacle in the large veins of the neck the effect of regurgitation is prevented. Broman,[23] in experiments with microemboli, reported the following extraordinary discrepancy: In direct observations on the living brain, he was unable to recognize any signs of the so-called brain purpura, whereas in microscopic examination of the postmortem material he could readily demonstrate ring hemorrhages. Between these two examinations the animals were subjected to all those hemodynamic disturbances which occur at the moment of cardiac arrest, when they were killed.

The ideas presented here have a few practical implications. The effusions of blood being explained as the result of an agonal passive process, the hemorrhages are not the expression of hemorrhagic diathesis, even if they are as numerous as in brain purpura! At the stage of dissemination of fat emboli, typical petechiae are presented in the skin (Benestad [43]), but simultaneously minute necrotic foci develop in the cerebral white matter. The minute necrotic foci were transformed into the typical ring hemorrhages if the patient died shortly after the accident. In experiments already referred to, Broman [23] found that minute emboli elicited alterations of the vascular permeability. He observed that in prolonged experiments the degree of vascular permeability increased and in the brain the hemorrhagic appearance of the lesions became more intense. A large number of minute hemorrhages were present in animals which survived from 8 to 12 days, whereas at later stages, when the vessels recovered from their condition of pathological permeability, the number of hemorrhages decreased. This critical period of both increased vascular permeability and hemorrhagic tendency was confirmed in similar experiments of microembolism performed by Swank and Hain.[44] All these observations indicate that a coincidence of agonal backflow of venous blood and physical change in the wall of the veins is essential for the production of the agonal effusions of blood, the number of which varies with the intensity and duration of action of the noxious agent.

SUMMARY AND CONCLUSIONS

The ring hemorrhage in the cerebral white matter comprises (1) centrally, a fully developed focal necrosis; (2) rupture of the wall of the small vessel passing

42. Dahl, B.: Duret-Bernerske blödninger, Norsk mag. lægevidensk. **98**:1347-1372, 1937; Pathologisch-anatomische und experimentelle Untersuchungen über die sog. Duret-Bernerschen Blutungen, mit besonderer Berücksichtigung ihrer gerichtlich-medizinischen Bedeutung und ihrer Beziehungen zur Commotio cerebri, Deutsche Ztschr. ges. gerichtl. Med. **29**:366-398, 1938.

43. Benestad, G.: Drei Fälle von Fettembolie mit punktförmigen Blutungen in der Haut, Deutsche Ztschr. Chir. **112**:194-205, 1911; Tre tilfælder av fettemboli med punktformige blödninger i huden, Norsk mag. lægevidensk. **3**:1-18, 1911.

44. Swank, R. L., and Hain, R. F.: Effect of Different Sized Emboli on the Vascular System and Parenchyma of the Brain, J. Neuropath. & Exper. Neurol. **11**:280-299, 1952.

into the central necrosis; (3) an encircling zone of intact red blood cells, and (4) preserved myelinated fibers, intact axons, and normal glia within the zone of hemorrhage.

According to the hypothesis explaining these morphologic features, the ring hemorrhage is due to the sudden disturbance of blood flow following cardiac arrest. In this period, the impact of regurgitated venous blood initiates a sudden increase in the pressure of the blood on the walls of the small veins and venules. Where the walls of the vessels have lost their resistance to this impact, the backflow of venous blood may cause rupture, with leakage of blood into the perivascular tissue. The leakage is halted when the venous backflow is diminished.

NEURAL TOXICITY IN TUBERCULOUS PATIENTS TREATED WITH ISONIAZID (ISONICOTINIC ACID HYDRAZIDE)

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IN THIS communication is reported a new syndrome of neural toxicity encountered in a group of tuberculous patients under treatment with isoniazid (isonicotinic acid hydrazide). Although foreshadowed, perhaps, in some of the few papers on the use of the drug in humans, the fully developed syndrome apparently has not previously been encountered or described, and no suggestion of it has appeared in the animal toxicity studies. The patients all had advanced pulmonary tuberculosis and had received a large quantity of the drug. We have examined in detail 14 patients from a larger group of 46 with similar complaints observed in a series of 408 patients receiving the drug.

The first complaint was that of a sense of numbness, or lack of feeling, and a tingling, "pins and needles," sensation in the toes and feet, as though the extremity had "been asleep" or was "thawing out from cold." If the drug was withdrawn at this point, the symptoms resolved in a few days. If the drug was continued, the disturbance spread up the legs to the knees, and then, in a few instances, the hands and fingers were similarly affected. As the process advanced, pain and ache in the skin and muscles were experienced, sometimes with a burning quality. This was increased by use of the limbs, and in two patients it became severe enough to prevent weight bearing and to interfere with sleep. At this stage the symptoms failed to subside promptly when administration of the drug was stopped. Four patients complained of an electric shock sensation when the limb was touched or moved. Muscular soreness or drawing pain in the calves was another complaint. Two patients also noted loss of balance, and two had weakness of the lower extremities. On the whole the sensory complaints dominated the picture, and ataxia and weakness were secondary in importance to the continual and disagreeable, if not actually painful, paresthesias of tingling and of burning pain. Nevertheless, the pain was not severe except in two instances, and the patients did not seek analgesics.

The location of these aches and pains lay below the knees and in the fingers and hands—in the familiar stocking-glove distribution. The process was bilaterally symmetrical.

No bladder or rectal symptoms, no visual symptoms, and no convulsions were encountered. No symptoms referable to the cranial nerves were noted. Several patients complained of dyspnea, and one had transitory dizzness, a symptom previously reported.

Examination revealed sensory and motor involvement in the distal part of the extremities, almost exclusively in the lower ones. In the earliest stages touch, pain, and temperature sensation was decreased in the toes and onto the dorsum of the feet. These defects gradually spread up the legs to the knees and became more complete, ending in loss of these cutaneous modalities. Dysesthesia to any stimulus was noted in over half the patients, and severe hyperalgesia was noted in one. Three showed deep muscular tenderness. Positional sense was not appreciably

TABLE 1.—*Signs of Isoniazid Toxicity in Fourteen Patients*

Case No.	Decreased Temperature, Pain, Touch	Dysesthesia	Deep Muscle Tenderness	Impaired Vibratory Sense	Decreased or Lost Achilles Reflex	Hyperactive Patellar Reflex	Decreased or Lost Patellar Reflex	Weakness
1	±	±	..	±	..	+	..	..
2	..	..	..	..	..	..	..	..
3	+	+	+	..	+	..	..	..
4	±	..	..	..	..	..	..	..
5	+	..	..	..	+	..	..	..
6	±	±	..	..	±	..	..	+
7	±	..	..	..	±	+	..	+
8	++	+	..	..	±	+	..	+
9	++	+	±	..	+	..	++	±+
10	++	±	..	..	+	..	+	..
11	++	±	..	..	+	+	..	+
12	++	+	±	..	+	+	..	+
13	+	..	..	..	+	..	..	..
14	++	..	..	±	±	+	..	+

TABLE 2.—*Neural Symptoms in Isoniazid Toxicity*

Case No.	Dose, Mg./Day	Tingling	Pain and Ache	Burning	Sense of Electric Shock	Soreness of Muscles	Loss of Feeling	Loss of Balance	Weakness
1	700	..	+	..	..	..	+	..	..
2	Inhalation (0.1-2 hr.)	±	..	..	..	..	+	..	..
3	450	±	..	..	..	..	+	..	..
4	600	+	..	..	..	..	..	..	..
5	550	+	..	..	..	..	+	..	..
6	300	±	..	+	..	+	±	..	..
7	750	+	+	..	..	+	±	..	..
8	700	+	++	++	..	..	+	..	..
9	650	+	+++	++	..	..	+	..	..
10	750	++	++	..	+	..	+	..	..
11	750	++	..	..	+	..	++	..	..
12	550	+	++	+	++	..	+	+	..
13	350	+	±	..	..	..	..	±	+
14	550	+	..	..	+	..	++	..	±

altered, and only two patients showed moderate diminution of the vibratory sense. Muscle weakness was minor in all but one patient. It was noted first in toe movements and then in plantar flexion and dorsiflexion of the feet. None of these patients had a complete foot drop, and all but one could walk, the latter apparently being disabled from burning dysesthesia, rather than from weakness. Weakness of the hands was not noted. Ataxia or incoordination was not observed despite a subjective complaint by two patients. The Romberg sign was not elicited.

In the patients with moderate or severe sensory impairment reflex changes were found. A decrease or loss of the Achilles reflex was noted in 12 patients;

the plantar reflex was lost in 6. The knee jerk was hyperactive in six patients, a sign previously noted, and was lost in two. Atrophy was not detected, and fascicular twitching was not observed. Chronaxie measurements, by Dr. William Erdman, were reported as normal in three patients, including the most disabled one. In some patients coldness and slight cyanosis of the feet were noted, but arterial pulses were good. No other neural abnormalities were revealed. A few patients had dsypnea, and one had transitory vertigo. No soreness of the tongue or significant uremia or jaundice was noted.

The distal involvement, the stocking anesthesia, and the absence of distal reflexes all suggest the development of a peripheral neuropathy. The sensory component dominated the complaints and the objective signs; yet definite, if minimal, motor weakness was observed as well. Vibratory and positional sensation was much less affected than touch, pain, and temperature sensibility.

If the concept of a peripheral neuropathy is correct, the condition may be compared with the clinical picture of other types of neuropathy. The predominant sensory complaints suggest an analogy with arsenical neuropathy, alcoholic neuropathy, and the rare trinitrotoluene neuropathy. Except in two instances the pain was distinctly less severe than in most cases of alcoholic neuropathy; yet foot drop was perhaps less frequent. The resemblance to arsenical neuropathy is perhaps closer, chiefly because of the predominant sensory disturbance and the degree of pain. Somewhat similar complaints have been encountered in trinitrotoluene poisoning—pains; paresthesias; and decreased pain, temperature, and touch sense without loss of vibratory sense. Dyspnea is also noted in that condition.

The question arises whether this condition represents a form of nicotinic acid deficiency. Before this question is considered, the reports on toxicity should be briefly reviewed. Animals (mice, rats, rabbits) given a single lethal dose died promptly in clonic convulsions with respiratory failure. Dogs showed salivation, vomiting, and anxiety preceding the fits. Chronic toxicity studies on rats showed anemia with leucocytosis and gross pathologic changes in the liver, kidney, spleen, and bone marrow. The total hemoglobin and oxyhemoglobin contents were decreased.[1] In dogs, anorexia, loss of weight, ataxia, body tremors, convulsions, and jaundice were noted. The symptoms were noted with doses of 4 mg. or more per kilogram of body weight and when the blood level rose to 6 or 8 γ per milliliter.[2] Reinhard and associates[3] did not observe any effect on blood pressure, respiration, or intestinal strips in dogs, or the uterus of the guinea pig, or on the tracheal cilia or gastric mucosa of the rat. Phenobarbital protected against the convulsions.[4] The drug protected against bronchospasm of cholinergic drugs, but not against histamine. No action on the muscle-nerve preparation or on ganglion blocking was noted.[1]

1. Benson, W. M.; Stefko, P. L., and Roe, M. D.: Pharmacologic and Toxicologic Observations on Hydrazine Derivatives of Isonicotinic Acid (Rimifon, Marsilid), Am. Rev. Tuberc. **65**:376, 1952.

2. Rubin, B.; Hassert, G. L.; Thomas, B. G. H., and Burke, J. C.: Pharmacology of Isonicotinic Acid Hydrazide (Nydrazid), Am. Rev. Tuberc. **65**:392, 1952.

3. Reinhard, J. F.; Kimura, E. T., and Schachter, R. J.: Some Pharmacologic Characteristics of Isonicotinyl Hydrazide (Pyricidin): A New Antituberculosis Drug, Science **116**:166, 1952.

4. Plan, S. Y.; Markaroglu, L., and Reilly, J.: Effects of Barbiturates on Toxicity of Isoniazid (Isonicotinic Acid Hydrazide), Am. Rev. Tuberc. **66**:100, 1952.

In man, Robitzek and Selikoff [5] reported symptoms which are undoubtedly the initial phase of the disability; the most frequent were twitching of the extremities, increased deep reflexes, vertigo, and constipation. Other, infrequent, symptoms were weakness of the legs, tinnitus, drowsiness, headache, insomnia, dryness of the mouth, myopia, delay in starting the urinary stream, and dyspnea. The dose ranged from 2 to 10 mg. per kilogram of body weight. Symptoms appeared in the second week and declined after the fourth week despite continuation of the drug. An epileptic patient died in status (Fetterhoff, Holmes, and Martin [6]). Sensitization to drug action was reported, e. g., epinephrine, ephedrine, atropine, and meperidine (Demerol).[7] One patient given meperidine exhibited generalized rigidity.

It is interesting that none of these observations on animal or human toxicity show any resemblance to the classic nicotinic acid deficiency syndrome. Our patients likewise had nothing that has been attributed to that state. The effect of the drug on tubercle bacilli is not counteracted by nicotinic acid.[8] It is of interest, however, that some other nicotinic acid analogues show an inhibitory activity on tubercle bacilli, e. g., picolinic acid (Bernstein and associates [9]); yet nicotinic acid hydrazide was inactive. The hydrazide grouping of the pyridine monocarboxylic series tested was necessary, for the corresponding amide and hydroxamic acid were inactive (mouse).

It is not known from animal or human investigation whether the action of this drug is antagonized by nicotinic acid. In our own cases it is not known whether nicotinic acid antagonized the toxic effect, for in all cases of severe poisoning the drug was stopped at the time nicotinic acid was administered. However, two patients noted improvement on treatment with large doses of the order of 400 mg., but not on smaller (100 mg.), on two occasions.

The implication from the work cited is that this drug does not produce a syndrome of nicotinic acid deficiency. The neuropathy, therefore, cannot on present evidence be laid to the antimetabolite action of this compound on nicotinic acid.

The dose range of doses in this study was at the level which produced toxic symptoms in other patients. The dosage schedule was to give 50 mg. of isoniazid (Pyrizidin) three times a day (150 mg. a day) and to increase the amount at one- to three-week intervals to 300, 450, 600 mg., etc., until the sputum was free of bacilli or toxic symptoms developed. The symptoms appeared in one to two weeks of the time administration of the particular toxic dose for the patient was begun. The factors of time and dose level both increased in this method of administration, and it is therefore impossible to separate them. For these patients the

5. Robitzek, E. H., and Selikoff, I. J.: Hydrazine Derivatives of Isonicotinic Acid (Rimifon, Marsilid) in Treatment of Active Progressive Caseous-Pneumonic Tuberculosis: A Preliminary Report, Am. Rev. Tuberc. **65**:402, 1952.

6. Fetterhoff, K. I.; Holmes, C. X., and Martin, G. E.: Hazards of Isoniazid Therapy in Epileptics: Report of a Case, Am. Rev. Tuberc. **66**:501, 1952.

7. Canada, R. O., and others: American Trudeau Society: Developments in Antimicrobial Therapy of Tuberculosis, Am. Rev. Tuberc. **66**:251, 1952.

8. Winterscheid, L.: Personal communication to the authors.

9. Bernstein, J.; Lott, W. A.; Steinberg, B. A., and Yale, H. L.: Chemotherapy of Experimental Tuberculosis: Isonicotinic Acid Hydrazide (Nydrazid) and Related Compounds, Am. Rev. Tuberc. **65**:357, 1952.

dose ranged from 4.5 to 13.5 mg. per kilogram a day, only four receiving less than 8 mg. No obvious correlation between dose and severity of symptoms could be noted; yet it appears likely that the neuropathy here reported resulted from the increased dose level.

This process easily clears if use of the drug is stopped unless it has progressed to obvious weakness; even then the symptoms may clear, but in a longer time. The neuropathy therefore puts a clear, but not serious, limitation on therapy, since the process probably does not produce permanent paralysis. It is possible, however, that in some cases the drug will prove more toxic to the patient than to his tubercle bacilli.

Little can be concluded from this study concerning the therapy of this toxic manifestation. It was found in the earlier stages, of minimal numbness and tingling, that withdrawal of the drug would cause fairly prompt cessation of symptoms. Later this was not the case. Many patients could be put back on treatment with the drug without redevelopment of the symptoms, while some might have recurrence of symptoms after weeks of resumption of the drug. There was suggestive evidence only that large doses of nicotinic acid (300 to 400 mg. a day) might be helpful in alleviation of symptoms.

SUMMARY

Of 408 patients with advanced pulmonary tuberculosis treated with isoniazid (Pyrizidin), 46 exhibited signs of peripheral neuropathy which one of us (F. W. B.) had not previously encountered with this drug. Fourteen were examined in detail. Tingling or painful paresthesias of the feet and legs were followed by weakness or paralysis, with loss of deep reflexes first at the ankles and then the knees. The hands were affected in a few instances. The process was subacute and subsided promptly on withdrawal of the drug unless it had progressed to a severe stage; in that case several weeks were required for even partial recovery.

The dose which induced these signs varied from 4.5 to 13.5 mg. per kilogram of body weight and was in the range in which toxicity is to be expected. The neuropathy puts a clear limitation on therapy with higher doses.

Since this paper was presented, peripheral neuropathy has been mentioned as a toxic side-effect of therapy with hydrazide derivatives of isonicotinic acid. No details of the cases were reported.[10]

ILLUSTRATIVE CASE

L. L. (Case 9), a Negro woman aged 39 with fibrocavernous pulmonary tuberculosis, was started on treatment with Rimifon (a brand of isoniazid) on March 12, 1952, in a dosage of 5 tablets (250 mg.) daily, then 10 (500 mg.) daily. Medication was changed to another brand of isoniazid (Pyrizidin) on May 13, in a dose of 350 mg. a day, which was increased to 450 mg. daily on May 20.

The patient thought that she first had numbness and tingling in late May or early June but that these symptoms cleared if she omitted taking the drug for one or two days. On June 25, the dose was increased to 500 mg., and then to 650 mg. on July 10. It was discontinued for two days on July 16 and July 18, with only slight decrease in symptoms. Numbness and tingling continued, but the drug was increased to 750 mg. on Aug. 7. She then had severe sharp and burning pains in her feet. Oral use of the isoniazid was discontinued on Aug. 30, and inhalation therapy with the drug was started. The pain and numbness became worse, with spread of sensory impairment to the knees and involvement of the hands.

10. Selikoff, I. J.; Robitzek, E. H., and Ornstein, G. D.: Treatment of Pulmonary Tuberculosis with Hydrazide Derivatives of Isonicotinic Acid, J. A. M. A. **150**:973, 1952.

All medication was discontinued on September 15. Neurological examination revealed decreased touch, pain, and temperature sensibility of the feet and lower legs with dysesthesias and a slight decrease in these sensations in the hands (fingers). Positional sense was intact. Vibratory sense was slightly impaired in the feet, but not lost.

There was definite weakness of dorsiflexion and plantar flexion of the feet and of the toe movements, with apparent bilateral foot drop. All movements were restricted by the pain, and she could not bear her weight; gait therefore was not tested. Cranial nerve function was impaired.

She was hospitalized, and treatment was started with nicotinic acid, 200 to 400 mg. given parenterally and by mouth daily; thiamine hydrochloride, 25 mg. three times a day; riboflavin injected parenterally; brewer's yeast, and liver extract. There was no improvement; all medication but the nicotinic acid was discontinued, and a multivitamin preparation was added on Oct. 6. All medication was discontinued on Oct. 22.

When she was examined on Oct. 6, the patellar, Achilles, and plantar reflexes were absent, with definite weakness of plantar flexion and dorsiflexion of the ankles and toes, as well as weakness of flexion and extension of the legs. Pain, touch, and temperature senses were decreased from the knees downward, accompanied by dysesthesias. Positional and vibratory senses were intact.

Examination of the spinal fluid on Oct. 6 showed clear and colorless fluid, 2 lymphocytes per cubic millimeter, and 42 mg. of protein per 100 ml. The Kolmer reaction was negative.

At a recent examination of the patients, on Nov. 6, approximately two months after isoniazid was discontinued and six months after appearance of the first symptoms, she complained of numbness of the lower third of the legs and pain in the feet of a sharp and aching character. She was able to walk.

Examination showed that the decreased sensation for pain and temperature involved the lower third of the legs and the feet. There were no dysesthesias. Definite, but minimal, weakness was still present. The patellar reflex was present but decreased; the plantar and Achilles reflexes were still absent. Chronaxie measurements made at this time were normal.

EFFECT OF RETROCHIASMAL LESION UPON VARIABILITY OF THE ABSOLUTE VISUAL THRESHOLD

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THIS PAPER presents data which show that the absolute visual threshold for light perception is significantly affected by processes other than retinal photochemistry. Specifically, it will be suggested that fluctuations in the absolute visual threshold are, in part, determined by neural factors. Such a suggestion is consonant with the view that threshold variability reflects physiological fluctuation and not fluctuation in the quantal emission by a stimulus. In other words, it will be maintained that threshold variability lies within the organism and not within the stimulus.

This point of view has been championed by Crozier [1] in relation to vision, but it is not held universally. For example, after demonstrating that only one quantum need be absorbed by only 5 to 14 rods of the human retina to produce the visual threshold event in the fully dark-adapted eye, Hecht, Shlaer, and Pirenne [2] concluded that "at threshold it is the stimulus which is variable, and that the properties of its variation determine the fluctuation found between response and stimulus." Impressed by the small number of random events initiating the photochemical changes related to the visual threshold, these authors also stated:

> At threshold where only a few quanta of energy are involved, it is the stimulus which is variable, and the very nature of this physical variability determines the variation encountered between response and stimulus. Moreover, even when biological variation is introduced, it is the physical variation which essentially dominates the relationship.

Such conclusions would seem to preclude threshold variability related to the numerous neural processes concerned with visual performance and to set the visual process apart from other sensory modalities, for which it has been demonstrated that lesions of the central nervous system increase threshold variability. Thus, it is the object of this study to analyze the threshold variability in patients with lesions limited to the neural components of the visual system. The particular lesions under

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The data presented in this paper were collected when the author was a Postdoctorate Fellow of the United States Public Health Service at the New York University College of Medicine.

1. Crozier, W. J.: On Visibility of Radiation at Human Fovea, J. Gen. Physiol. **34**:87, 1950.

2. Hecht, S.; Shlaer, S., and Pirenne, M. H.: Energy, Quanta, and Vision, J. Gen. Physiol. **25**:819, 1942.

consideration produce a defect commonly described as hemianopsia, or complete loss of vision, in homonymous halves of the visual fields. However, this loss is not necessarily complete, a previous publication [3] having described residual function in these so-called blind half-fields. To elicit this function, it is necessary to examine the fields with a luminous target in total darkness after a period of dark adaptation. Under such conditions it is possible to measure variations in the absolute visual threshold of these so-called blind fields.

MATERIAL AND METHOD

Six patients, whose histories are presented in Table 1, were studied. The field defects were demonstrated by routine perimetry under 7 foot-candles (f.-c.) of illumination. Ophthalmoscopic examination showed all the retinas to be normal.

TABLE 1.—*Pertinent Perimetric and Historical Data*

Patient	Age, Yr.	Perimetric Fields	Clinical History
A. F.	39	Left homonymous hemianoptic defect with 8° macula sparing	Right occipital subdural hematoma; right third nerve paresis (transient) Etiology: Presumably traumatic
M. F.	42	Left homonymous hemianoptic defect with 5° macula sparing	Right subdural hematoma, with transient, mild, right-sided paresis and bilateral hyperreflexia Etiology: Never clearly established; known to be alcoholic, with rheumatic heart disease and signs of subacute bacterial endocarditis
M. E.	18	Right homonymous hemianopsia with 18° to 20° macula sparing	Sudden onset of homonymous hemianopsia; unaccompanied by other signs or symptoms Etiology: Unknown
H. G.	66	Bilateral, almost complete, homonymous anopia with some vision remaining to either side of midline of inferior quadrants of both visual fields	Sudden onset of dizziness, blindness, and nonpsychotic visual hallucinations in 1944; mild improvement in vision Etiology: Unknown
S. R.	30	Left peripheral homonymous hemianoptic field defect; spontaneous clearing	Rheumatic heart disease in childhood; in 1947, hemoptysis and transient left hemiparesis; in 1949, carbon monoxide poisoning reprecipitated left hemiparesis, which was accompanied by left hemisensory syndrome with hemianopsia; gradual, incomplete recovery in all spheres; no apparent visual defect remaining
M. M.	18	Homonymous hemianopsia; spontaneous recovery	Sudden onset of diplopia followed by hemianopsia Etiology: Congenital syphilis; complete remission during therapeutic course; mild exacerbation 2 mo. later

After these preliminary examinations, the patients' absolute visual thresholds were determined essentially by the technique of Hecht and Shlaer. The apparatus used was Wald's portable adaptometer,[4] arranged so that the target could be placed at any point in the visual field at 27 cm. from the eye. This luminous target was a circle subtending 2½ degrees of retinal angle and exposed for 1/25th second. The ocular fixation point was a just visible pinpoint of red light. The head was fixed to the apparatus. Precautions were taken to eliminate extraneous clues by presenting the target in a homogeneous, black, nonreflecting field within the otherwise absolutely dark room. The pupils were not treated with drugs, and one eye was covered while the other was examined.

This study was limited to the evaluation of the absolute visual threshold when the dark-adaptation process had come to an end for practical purposes. For determination of this threshold and its variability, the patient was placed in a dark room, and dozens of threshold measurements were made. Prior to being dark-adapted, the patient was in one of two states of light adaptation.

3. Bender, M. B., and Krieger, H. P.: Visual Function in Perimetrically Blind Fields, A. M. A. Arch. Neurol & Psychiat. **65**:72, 1951.

4. Wald, G.: Portable Visual Adaptometer, J. Optic. Soc. America **31**:235, 1941.

Either he had been light-adapted by ordinary room light or by 1,500 millilamberts diffused over 50 degrees of retinal angle for five minutes. The previous state of light adaptation had only a temporal effect upon the final level of dark adaptation; the greater the degree of preliminary light adaptation, the longer it took to reach the final level of dark adaptation, this level being the same regardless of the antecedent state of light adaptation. The threshold was measured in micromillilamberts and expressed in logarithmic units. Graphic representation of the thresholds, as determined serially, gave either the complete dark-adaptation curve or just its tail, depending upon the previous state of light adaptation.

The controls were of two sorts, the patient himself and the data of other workers in the field of dark adaptation. In all the patients the hemianopsia created a condition whereby it became possible to compare two symmetrical parts of the nervous system, one normal in function and one defective, yet both incorporated within one eye. Ordinarily, symmetrical nervous system structures have symmetrical functions. Thus, a difference in function between two halves of the visual field of one eye may be regarded as significant. Furthermore, the function of the unaltered halves of the fields of the patients fell within the normal limits as those defined by Hecht and his students.[5] This fact was a second method of control. A third method of control could be applied only to the patients who recovered function in the defective field. In such patients defective function was compared with recovered function within the half-field which was affected by the disease process, while both these functions were, in turn, compared with the normal half of the field of the same eye. The fourth method of control was to examine the functions in question repeatedly over periods as long as 15 months. This supplied a measure of consistency of the results and demonstrated that the changes noted were not significantly altered by learning what occurred during the studies.

RESULTS

Two types of representative cases were found. First, there were those in which, in the defective field, the threshold was raised and had increased variability. In these cases the hemianopsia was permanent; they may be illustrated by the case of A. F. In Chart 1 will be found her perimetric fields and dark-adaptation curves taken at 20 degrees from the fovea along the four principal 45-degree meridians of each eye. The final thresholds in the defective fields were 500 to 1,500 times as high as those at analogous points in the normal fields. The method of control used in this study eliminates the necessity for statistical assessment of the significance of this threshold difference. Furthermore, in addition to the rise in threshold in the defective field, there was a greater degree of variability in the final threshold of the defective regions, as compared with that in analogous normal regions. It should be noted that these differences could not be due to learning, since the same changes in both the value and the variability of the threshold were found repeatedly over the course of 15 months.

The second type of representative case was characterized by recovery from a hemianopsia. In these cases the mean threshold was normal, but there were pronounced changes in the variability about this mean. These findings are illustrated in Chart 2, showing the values for S. R. Note that, although the mean threshold in the defective regions was within normal limits throughout the illness, the variability of this threshold gradually decreased during the recovery period. Ultimately, no defect was found on perimetric determination or in the mean and variability of the threshold of the previously defective half-field.

5. Hecht, S., and Shlaer, S.: Adaptometer for Measuring Human Dark Adaptation, J. Optic. Soc. America **28**:269, 1938. Mandelbaum, J.: Dark Adaptation: Some Physiologic and Clinical Considerations, Arch. Ophth. **26**:203, 1941.

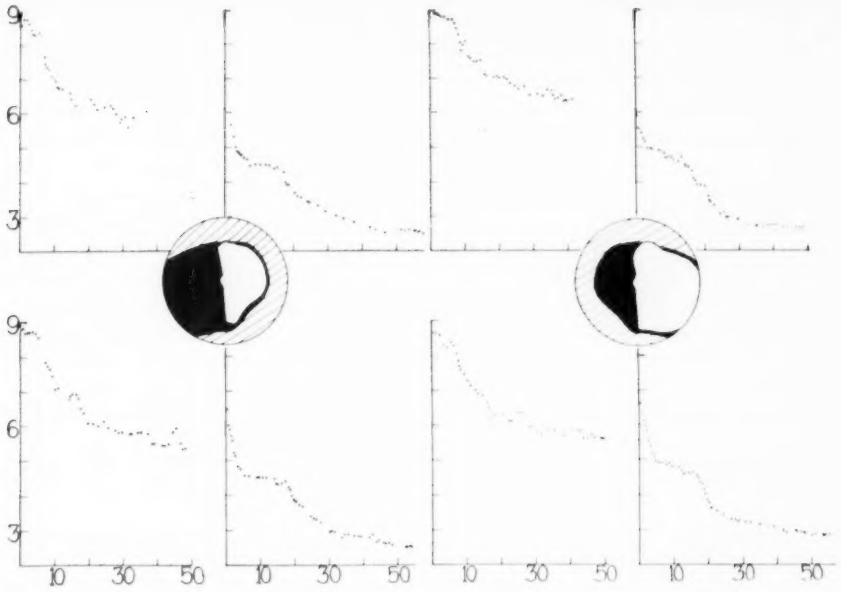

Chart 1 (A. F.).—Dark-adaptation curves illustrating the greater degree of variability in the absolute visual threshold of perimetrically defective areas than in that of analogous normal areas. Each curve was measured at 20 degrees from the fovea along the 45-degree meridian. The four curves to the left were measured in the left eye, and the four to the right, in the right eye. The blacked-out areas of the visual-field charts represent the areas of blindness, as determined by routine perimetry. Abscissas are in minutes; ordinates, in logarithms of the absolute visual threshold measured in micromillilamberts.

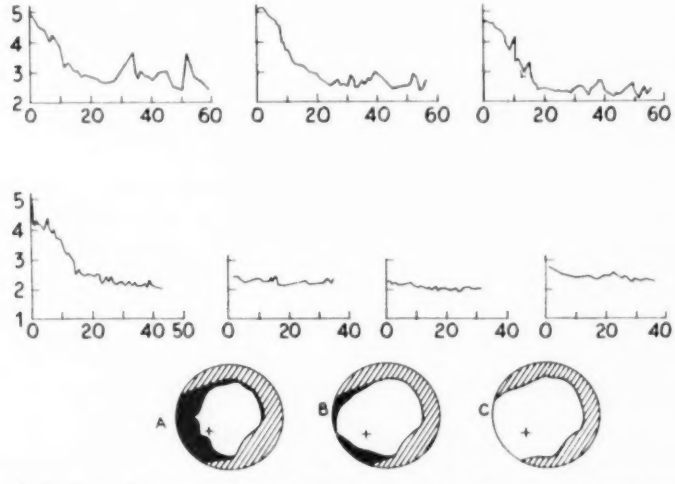

Chart 2 (S. R.).—Changes in the variability of the absolute visual threshold and the perimetric fields during recovery from a homonymous hemianopsia. The curves were measured at the + mark in the visual fields at varying intervals during the course of recovery. The blacked-out areas on the visual-field charts represent the blind areas, as determined by standard perimetry. Note that whereas the first four curves were measured after a period of 1,500 millilamberts of light adaptation, the last three were measured after exposure to room light. Abscissas are in minutes; ordinates, in logarithms of the absolute visual threshold measured in micromillilamberts.

A representative statistical analysis will be found in Table 2 in the case of S. R. If it is assumed that after about 25 to 30 minutes in the dark visual adaptation proceeds at a rate so slow as to be an asymptotic function, the degree of threshold variability may be expressed in terms of its variance (σ^2). Fisher's z test may then be used to assess the significance of the difference between any two variance values. By this method, the difference between the variance of the threshold of the defective area on Dec. 3, 1948, and the variance of the same point one month later was found to be significant at much less than the 1% level of confidence. By Jan. 3, 1949, the variance of the threshold of this previously defective point was within the range of the variance of the nondefective analogous points within the same eye, and also of analogous points in the normal half of the other eye. In this second group of cases, the recovery from the hemianopsia allowed a given retinal point to be

TABLE 2.—*Standard Deviation and Estimated Variance of Absolute Visual Threshold of Points* in Normal and Defective Visual Fields of S.R.*

Left Eye: Defective Area; Meridian 225°; Arc 45°

Date	σ	σ^2	N†
12/3	0.4561	0.2202	18
12/6	0.17861	0.033126	27
12/8	0.1769	0.032600	25
12/16	0.08544	0.007684	20
12/22	0.10000	0.014540	23
12/29	0.03873	0.001583	19
1/3	0.09434	0.00889	19

Controls, Normal Area

	Left Eye					Right Eye			
Date	Meridian Arc	σ	σ^2	N	Date	Meridian Arc	σ	σ^2	N
12/1	45°/20°	0.1414	0.025	6	12/16	225°/45°	0.05099	0.00288	10
12/1	135°/20°	0.1414	0.0228	8	12/16	315°/45°	0.08802	0.00802	13
12/6	315°/45°	0.05099	0.002817	13	12/22	225°/45°	0.05568	0.00344	10
12/8	135°/45°	0.1025	0.0112	16	12/22	315°/45°	0.06164	0.00418	11
12/10	315°/30°	0.06633	0.00458	26					
12/10	45°/30°	0.1109	0.01268	33					
12/22	315°/45°	0.09055	0.00895	12					

* Note the change in these values during recovery of visual function in the defective field.
† N indicates number of measurements made.

examined before, during, and after recovery. In this respect, the trend of threshold variance of the defective area was in one direction during the recovery process.

In summary, the data of these two typical cases show that after damage to the visual system at a point behind the chiasm there is an increase in the variability of the absolute visual threshold with or without a concomitant rise in the mean threshold value. Furthermore, in those cases in which there is recovery of function, as judged by the results of perimetry, the degree of threshold variability declines as the perimetric defect recedes.

COMMENT

The interpretation of these results as indicative of increased fluctuation due to damage to the central nervous system requires the demonstration that there were no photochemical changes in the retina and that the defective nervous system mediated the impulses set up by the stimulus within the defective visual field. Since the patients had homonymous field defects, whereas their retinas appeared normal upon ophthalmoscopic examination, it was concluded that any changes in function

were related to retroretinal structural changes. This conclusion was substantiated by concomitant neurological signs and symptoms of disease of the central nervous system. There was no reason to suspect any changes in the photochemical system of the retinas, and retrograde photochemical changes subsequent to damage to the central nervous system have not been described.

It was more difficult to demonstrate conclusively that the visual response in the defective fields was mediated by the damaged visual pathways alone. For example, the roles of stray light within the eye and of retinal-neural interaction had to be evaluated. The observations justifying the conclusion that the responses recorded in this study were mediated solely over the defective visual pathways have been described in a previous publication.[3] Some of these observations may be noted: 1. The target was correctly localized within the defective field as far out as 90 degrees along the horizontal meridian of the defective field. To propose that such localization was the result of light straying over an area of 90 degrees of retinal angle along the horizontal meridian to the intact visual system would imply a contradiction in the assumed optical representation of the environment upon the retina and imply that any locus on the retina may allow localization within the entire visual field. 2. Upon recovery from the anopia, the thresholds reverted to normal without a subjective or an objective alteration in localizing ability within the formerly defective field. 3. After dark adaptation, a patient with almost complete bilateral hemianopsia could correctly locate the target within defective areas. Here, light straying across the midline was not necessary for this localizing ability. 4. A man with a nonretinal lesion was apparently completely blind upon examination in room light. However, he could appreciate light if he was allowed to remain in a dark room before being examined with a luminous target. 5. Battersby[6] showed that in some cases the target disappeared within the blind spot of an "anopic" field. He also found some hemianoptic patients in whom visual function could not be demonstrated in the defective half-field. Stray light and retinal-neural interaction were probably as operative in this group as in that which had some visual function in the defective areas. The last observation makes it improbable that stray light and retinal-neural interaction were important factors in the residual visual ability found in the hemianoptic areas of our patients.

Interpreting these observations as indicative of residual light perception in the defective half-fields, one asks the origin of the increased threshold variability demonstrated within such fields. One possibility would be that this increased fluctuation arises within the organism and is an expression of the combined function of both the damaged and the remaining normal tissues. This hypothesis, however, cannot be accepted without first considering Hecht's conclusions relative to the role of quantal variation of the threshold stimulus as the determinant of threshold variability.

For Hecht, threshold variability resulted from the small number of quanta reaching the photosensitive substance in the threshold event, while biological variation was discounted. According to this theory, any increase in the number of quanta of light reaching the retina should reduce threshold variability. In the patients with permanent hemianopsias the stimulus intensity had to be raised 500 to 1,500 times to reach threshold. Despite this increase in the number of quanta

6. Battersby, W. S.: Regional Gradient of Critical Flicker Frequency After Frontal or Occipital Lobe Injury, J. Exper. Psychol. **42**:59, 1951.

reaching the retina, threshold variability was increased in these patients. Even more significant in this respect were the changes in the threshold in patients who recovered visual function. It will be recalled that the mean of their absolute thresholds remained unchanged, while the variability of this index gradually declined as recovery progressed. For these patients, the mean stimulus intensity (or, in terms of energy, the average quantal emission of the stimulus) required for the threshold event remained unchanged; yet the degree of variability declined with recovery. This finding, namely, that the mean threshold and its variability may be independent functions after lesions in the central nervous system is not predictable from Hecht's concepts. However, such a finding is in accord with Crozier's statistical concepts of visual thresholds and corresponds with his observations on the effects of inhalation of 100% oxygen upon the frequency of seeing curve in the normal.[1]

CONCLUSION

This study shows that after damage to the central nervous system the source of increased variability lies within the organism. The data, however, do not afford a crucial test for assigning threshold variability in the normal to either the stimulus or the organism. But it should be noted that, whereas on the basis of Hecht's theory the results of this study could not have been predicted, the data are compatible with Crozier's theoretical concepts of visual thresholds.

SUMMARY

The variability of the absolute visual threshold for light perception was studied in the defective half-fields of hemianoptic patients. It was found that there was an increase in the variability of this threshold with or without a concomitant rise in its mean value. Furthermore, in those patients who recovered from the hemianopsia, the degree of variability declined as recovery progressed. It is concluded that the observed increased threshold variability after damage to the central nervous system arose within the organism. This conclusion is discussed in view of Hecht's theory that variability in the absolute visual threshold in the normal subject is only a reflection of variation in quantal emission by the stimulus.

EFFECTS OF AGING ON CEREBRAL CIRCULATION AND METABOLISM

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THE EFFECTS of normal aging on cerebral circulatory physiology are of interest for several reasons. Many of the disease states in which cerebral vascular and metabolic functions are studied are commoner in middle-aged and elderly persons, making statistical comparisons with normal groups, presently comprised almost entirely of young subjects, inaccurate. In addition, the alterations which occur in cerebral circulatory functions with advancing age may provide additional clues to the understanding of many clinical problems of the aged, particularly those related to vascular disease of the brain; and such studies may provide the physiologist with further information concerning general patterns of circulation in subjects of middle and old age. The purpose of this report is to record our observations in the use of the nitrous oxide technique for measuring cerebral blood flow on 32 normal men between the ages of 38 and 79. It is planned to continue these studies so that a pattern of change for the individual decades can be determined, and so that additional correlative observations can be made on the subjects studied.

PRESENT INVESTIGATION

Methods.—The subjects chosen for this study had been admitted to the hospital for minor elective operative procedures. All had been living normal lives consistent with their respective age group prior to admission, with no history to suggest any consequential pathology. An effort was made, by careful history taking and physical examination, to rule out significant clinical vascular disease, although some of the older subjects had such evidences of peripheral sclerosis as moderate thickening (to palpation) of the peripheral vessels, widening of the light reflex of the retinal arterioles, and occasional mild retinal arteriovenous nicking. In all instances the mental status was adjudged to be normal on the basis of a test pattern generally approved for gross psychological testing. Only those subjects whose arterial oxygen saturation was 94% or greater were considered acceptable; those whose oxygen saturation was below this value were considered to have respiratory disease, even though other evidence for it was lacking. The latter subjects will be discussed separately, in a subsequent publication. The

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criteria for normalcy were strict and rigidly adhered to, but, obviously, the presence of subclinical cerebral vascular disease could not be ruled out; indeed, this study probably measures its incidence.

Cerebral blood flow was measured by a modification [1] of the original nitrous oxide technique of Kety and Schmidt.[2] The subjects were fasting and without sedation. The method of the study was similar to that previously reported, in which observations were made on normal young adults.[1] The blood oxygen content was measured by the spectrophotometric technique of Hickam and Frayser.[3] Samples of blood for oxygen determination were drawn before and after each blood flow measurement, and the average was used as the final value for arterial-cerebral venous oxygen difference and arterial oxygen saturation. Cerebral venous oxygen tension was not measured directly but was computed from the percentage of oxygen saturation of cerebral venous blood by means of a standard oxyhemoglobin dissociation curve drawn for pH 7.3. Arterial pressure measurements were made by the auscultatory method every two minutes during the procedure, with the patient's arm held at heart level. Mean pressures were calculated from the formula

$$\text{MP} = \text{diastolic pressure} + \tfrac{1}{3} \text{ pulse pressure}$$

and in most patients the results agreed closely with the mean pressure measured directly by a mercury U-tube manometer.

Results.—A compilation of the data on all patients is given in Table 1, and a comparison of young with middle-aged and elderly normal subjects is given in Table 2. The cerebral blood flow varied from 33 to 82 ml. a minute per 100 gm. of brain, with a mean of 55 ml. a minute per 100 gm. This represents a 15% reduction from the mean value of 65 ml. obtained for normal subjects between the ages of 18 and 36.[1] The two groups were studied at different times but in the same manner. The values for arterial-cerebral venous oxygen difference varied from 3.8 to 9.3 vol. %, with a mean of 6.58 vol. %, a 10% increase from the mean of 6.01 vol. % for young normal subjects. Cerebral oxygen consumption varied from 1.4 to 5.2 ml. O_2 per minute per 100 gm. of brain; the mean value of 3.64 ml. does not differ significantly from the mean of 3.84 ml. for young normal subjects, though it certainly represents a trend toward reduction, as further division of the subjects according to age group has indicated.

Mean arterial pressure varied from 71 to 122 mm. Hg, with a mean of 96 mm. Hg, which is 14% greater than the mean of 85 mm. Hg found for normal young subjects. Analysis of values for cerebral blood flow for patients whose mean pressure was above 100 mm. Hg showed no difference from those for the remainder of the group, and since it has been shown that hypertension *per se* has no specific effect on cerebral blood flow,[4] the reduction in cerebral blood flow for the subjects in this study as compared with that for young normal subjects cannot be attributed

1. Scheinberg, P., and Stead, E. A., Jr.: Cerebral Blood Flow in Male Subjects as Measured by the Nitrous Oxide Technique: Normal Values for Blood Flow, Oxygen Utilization, Glucose Utilization, and Peripheral Resistance, with Observations on the Effect of Tilting and Anxiety, J. Clin. Invest. **28**:1163, 1949.

2. Kety, S. S., and Schmidt, C. F.: The Nitrous Oxide Method for the Quantitative Determination of Cerebral Blood Flow in Man: Theory, Procedure, and Normal Values, J. Clin. Invest. **27**:476, 1948.

3. Hickam, J. B., and Frayser, R.: Spectrophotometric Determination of Blood Oxygen, J. Biol. Chem. **180**:457, 1949.

4. Kety, S. S.; Hafkenschiel, J. H.; Jeffers, W. A.; Leopold, J. H., and Shenkin, H. A.: The Blood Flow, Vascular Resistance, and Oxygen Consumption of the Brain in Essential Hypertension, J. Clin. Invest. **27**:511, 1948.

TABLE 1.—*Cerebral Metabolic Functions in Normal Middle and Old Age*

Case No.	Age, Yr.	Cerebral Blood Flow, Ml./Min./100 Gm. Brain	Arterial-Cerebral Venous Oxygen Difference, Vol. %	Cerebral Oxygen Consumption, Ml. O_2/Min./100 Gm. Brain	Arterial Oxygen Saturation, %	Cerebral Venous Oxygen Tension, Mm. Hg	Mean Arterial Pressure, Mm. Hg	Cerebral Vascular Resistance, Mm. Hg/Ml. Blood/Min./100 Gm. Brain
1	38	57	4.9	2.8	96.4	38	97	1.70
2	43	78	5.9	4.6	97.4	36	94	1.21
3	44	60	6.2	3.7	95.5	32	104	1.74
4	45	63	6.3	4.0	96.2	31	92	1.46
5	46	61	6.4	3.9	96.0	43	91	1.49
6	49	48	5.5	2.7	94.5	37	79	1.65
7	50	66	6.7	4.4	95.8	32	97	1.47
8	50	61	6.3	3.8	94.1	29	108	1.77
9	52	63	6.1	3.9	95.9	34	94	1.48
10	53	58	6.3	3.6	95.4	32	95	1.64
11	53	59	7.1	4.2	96.0	30	79	1.34
12	54	53	8.1	4.3	96.4	26	109	2.06
13	55	57	7.4	4.2	98.6	29	110	1.93
14	55	64	8.1	5.2	96.4	29	89	1.39
15	55	69	8.0	4.8	96.9	29	94	1.57
16	56	38	3.8	1.4	95.5	44	82	2.16
17	57	47	6.5	3.1	95.7	31	107	2.28
18	58	47	6.5	3.1	97.2	31	90	1.91
19	58	74	6.5	4.8	95.2	32	79	1.07
20	59	50	6.1	3.1	96.3	31	99	1.98
21	59	52	7.7	4.0	96.5	29	86	1.66
22	59	52	7.2	3.8	96.1	32	109	2.10
23	60	42	6.5	2.7	95.6	33	98	2.33
24	62	82	6.2	5.1	94.9	30	71	0.87
25	62	33	7.3	2.4	98.7	31	101	3.06
26	62	58	6.1	3.5	99.4	34	100	1.73
27	62	46	6.0	2.8	95.2	31	89	1.94
28	63	39	5.6	2.2	96.2	38	92	2.35
29	65	56	7.1	4.0	96.6	31	122	2.18
30	69	55	6.4	3.5	94.8	30	122	2.22
31	74	50	6.4	3.2	96.4	30	114	2.28
32	79	40	9.3	3.7	97.2	29	94	2.35
Mean		55.3	6.58	3.64	96.2	32.3	96.5	1.82
Standard deviation		11.2	1.02	0.868	1.16	4.00	12.2	0.451
Standard error		1.97	0.180	0.153	0.206	0.707	2.16	0.080

TABLE 2.—*Comparison of Cerebral Vascular and Metabolic Functions* in Young and Middle-Aged and Elderly Normal Subjects (Mean Values)*

	Age			
	18-36 (19 Subjects)	38-79 (32 Subjects)	*P* Value	Change, %
CBF	65.3	55.3	< 0.01	− 15
A-VO_2	6.01	6.58	< 0.05; > 0.02	+ 10
$CMRO_2$	3.84	3.64	> 0.5	.....
MAP	84.9	96.5	< 0.01	+ 14
CVR	1.34	1.82	< 0.01	+ 36

* In this table, and in Tables 3 and 4, CBF indicates cerebral blood flow; A-VO_2, arterial-cerebral venous oxygen difference; $CMRO_2$, cerebral oxygen consumption; MAP, mean arterial pressure, and CVR, cerebral vascular resistance.

to the elevation in arterial pressure. Cerebral vascular resistance varied from 0.87 to 3.06 mm. Hg per milliliter of blood per minute per 100 gm. of brain, with a mean of 1.82 mm. Hg, an increase of 36% over the mean value of 1.34 mm. found for young normal subjects.

Arterial oxygen saturation varied from 94.1 to 99.4% with a mean value of 96.2%, which compares favorably with the mean of 96.4% reported by Greifenstein, King, Latch, and Comroe [5] for healthy subjects over 50 years of age. Cerebral venous oxygen tension varied from 26 to 44 mm. Hg, with a mean of 32 mm. Hg.

For purposes of further comparison, the subjects in this study were divided into two approximately equal age groups: (*a*) those from 38 to 55 and (*b*) those from 56 to 79 years of age (Table 3). There is a significant reduction in mean cerebral blood flow of 17% and in mean cerebral oxygen consumption of 17% in the elderly as compared with the middle-aged subjects. Cerebral vascular resistance is 28% higher in the elderly group. There were no significant differences in arterial-cerebral venous oxygen difference and mean arterial pressure in the two groups.

TABLE 3.—*Comparison of Cerebral Vascular and Metabolic Functions of Middle-Aged and Elderly Normal Subjects (Mean Values)*

	Age		
	38-55 (15 Subjects)	56-79 (17 Subjects)	*P* Value
CBF	60.5	50.6	< 0.01
A-VO_2	6.02	6.54	> 0.5
$CMRO_2$	4.01	3.32	0.02
MAP	95.5	97.4	> 0.5
CVR	1.59	2.03	< 0.01

If the values for the middle-aged subjects (38 to 55 years) are compared with those for young normal subjects, there are seen a tendency toward reduction of cerebral blood flow and a significant increase in arterial-cerebral venous oxygen difference, mean arterial pressure, and cerebral vascular resistance in the middle-aged group. There is no difference in cerebral oxygen consumption in the two groups.

There was no significant correlation between the electroencephalograms obtained on some of these subjects and measured cerebral metabolic values. Each of the groups of subjects breathed a mixture of 10% CO_2 and 90% O_2, which is known to increase cerebral blood flow greatly without altering the cerebral oxygen consumption in young subjects. On the basis of changes which occurred in arterial-cerebral venous oxygen difference, the cerebral blood flow in these subjects more than doubled in each instance.

COMMENT

The data presented here indicate that the cerebral blood flow is lower and the cerebral vascular resistance greater in normal middle-aged and elderly subjects than in normal young subjects. Table 4 summarizes the statistical analyses of

5. Greifenstein, F. E.; King, R. M.; Latch, S. S., and Comroe, J. H., Jr.: Pulmonary Function Studies in Healthy Men and Women 50 Years and Older, J. Appl. Physiol. **4**:641, 1952.

correlation between age and the various cerebral vascular and metabolic functions. Chart 1 depicts the relation between age and cerebral blood flow and indicates the progressive gradual reduction in cerebral blood flow with advancing age. Inspection of the distribution of the points suggests that the greatest reduction in cerebral blood flow begins at about the age of 50, with only a moderate decrease from the age of 18 to that of 50. The correlation between age and arterial-cerebral venous oxygen difference is similar to that between age and cerebral blood flow. Chart 2 depicts the correlation between age and cerebral vascular resistance; the same tendency for the curve to incline more steeply after the age of 50 is noted.

Chart 3 indicates the apparent lack of consistent correlation between age and cerebral oxygen consumption. That there is a progressive reduction in cerebral oxygen consumption past middle age, however, is indicated by the statistically significant difference in mean cerebral oxygen consumption between the middle-aged and the elderly group (Table 3).

The progressive reduction in cerebral blood flow appears to be related to progressive increase in cerebral vascular resistance, indicating that there is a reduction in the lumina of the cerebral vessels with advancing age, due either to progressive

TABLE 4.—*Correlation of Age and Cerebral Vascular and Metabolic Functions in Fifty-One Subjects**

	r Value	*P* Value
CBF	0.458	< 0.01
A-VO_2	0.370	< 0.01
$CMRO_2$	0.186	> 0.20
MAP	0.485	< 0.01
CVR	0.633	< 0.01

* The ages ranged from 19 to 79.

vascular sclerosis or to increase in vascular tone or to both. Since the nitrous oxide technique measures cerebral blood flow per unit weight of brain tissue, complete exclusion of a segment of the brain from the circulation would not affect the cerebral blood flow or metabolism, provided that the remaining brain tissue and its blood vessels were normal. Thus, the increase in cerebral vascular resistance with advancing age does not denote loss of tissue, but, rather, indicates increased resistance to flow of blood through the functioning vessels. That this progressive encroachment on the lumina of the cerebral vessels is not absolutely fixed is indicated by the great decrease in cerebral vascular resistance in eight of the patients which followed inhalation of 10% CO_2. Fazekas, Alman, and Bessman [6] noted a moderate increase in cerebral blood flow in subjects over the age of 50 with cerebral vascular disease when they breathed a gas mixture containing 5% CO_2, but pointed out that the vasodilatation was not as marked as it was in the younger subjects, reported by Kety and Schmidt.[7] The striking diminution in arterial-cerebral venous oxygen difference noted in our subjects after inhalation of 10% CO_2 would indicate that a sufficiently powerful stimulus is capable of dilating the cerebral vessels of elderly

6. Fazekas, J. F.; Alman, R. W., and Bessman, A. N.: Cerebral Physiology of the Aged, Am. J. M. Sc. **223**:245, 1952.

7. Kety, S. S., and Schmidt, C. F.: Effects of Altered Arterial Tensions of Carbon Dioxide and Oxygen on Cerebral Blood Flow and Cerebral Oxygen Consumption of Normal Young Men, J. Clin. Invest. **27**:484, 1948.

Chart 1.—Correlation of age and cerebral blood flow.

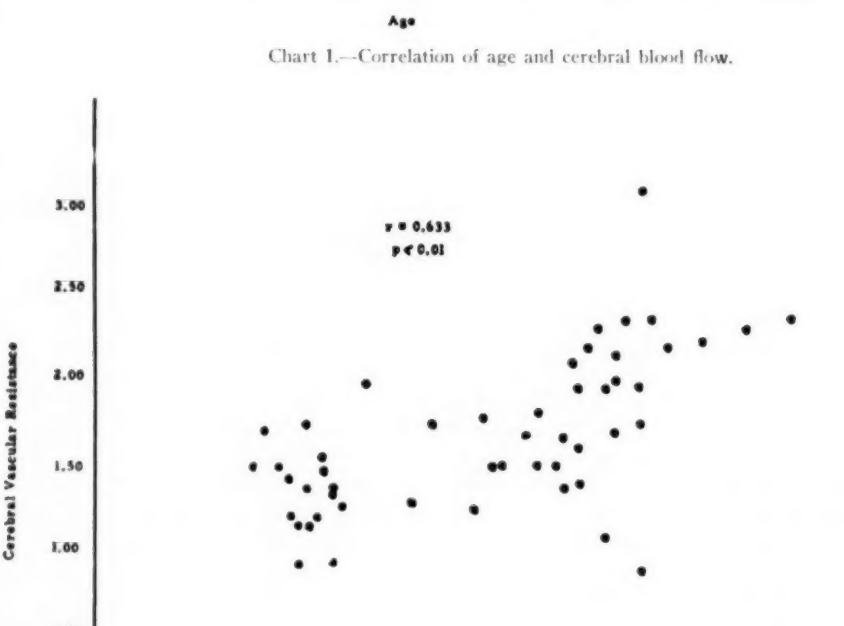

Chart 2.—Correlation of age and cerebral vascular resistance.

subjects. In addition, the relative lack of response in the group reported by Fazekas and associates may be related to the presence of known cerebral vascular disease.

The significant decrease in cerebral oxygen consumption in the oldest group in this study, as compared with the middle-aged and the young normal subjects, seems to be related to inability of the cerebral cells to extract increasing quantities of oxygen as the cerebral blood flow falls, for the mean arterial-cerebral venous oxygen difference for the elderly group remains the same as that of the middle-aged group, whereas cerebral blood flow is significantly reduced. This finding not only speaks for the presence of "subclinical" vascular disease in apparently normal elderly subjects, but also indicates that some reduction in the functional capacity of brain

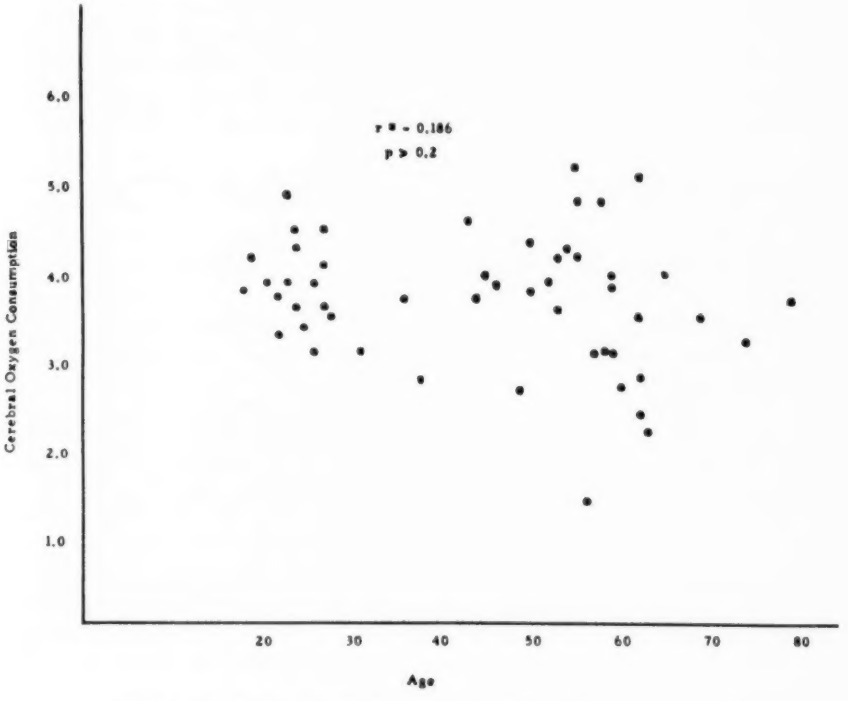

Chart 3.—Lack of correlation between age and cerebral oxygen consumption.

cells has occurred. In the presence of normal cell function, a reduction of blood flow of at least 21% may be completely compensated for by widening of the arterial-venous oxygen difference. Young subjects who stand motionless maintain normal cerebral metabolism in this way.[1] In heart failure a reduction in the cerebral blood flow of 40% is not completely compensated by widening of the arterial-cerebral venous oxygen difference,[8] but the mean difference (8.56 vol. %) is considerably greater than in the group reported here. The relative constancy of the cerebral arterial-venous oxygen difference in normal adults of all ages has previously been

8. Scheinberg, P.: Cerebral Circulation in Heart Failure, Am. J. Med. **8**:148, 1950.

reported by several workers and reviewed by Himwich,[9] but the absence of correlative studies on cerebral blood flow failed to indicate the progressive decrease in cerebral metabolism. This fact has previously been pointed out by Fazekas and his co-workers,[6] and in this sense our studies are in qualitative agreement with theirs.

The gradual reduction of cerebral blood flow and of cerebral metabolism during aging could be anticipated from clinical observations, as well as laboratory investigations on other organ systems. After the age of 60, the normal adult type of electroencephalogram is often replaced by tracings with slow-frequency waves.[10] The appearance of these slow tracings is thought to be due to cerebral vascular and metabolic alterations of old age, and the studies reported here confirm the occurrence of such changes. The subtle changes in mental function revealed in normal old age by careful psychologic testing may also be indicative of diminution in cerebral metabolism. Previous observers have noted the progressive reduction in renal blood flow [11] and cardiac output [12] which accompany the normal aging process, and tissue respiration studies have shown that liver, kidney, and cardiac muscle have a lower oxygen consumption with advancing age.[13] The studies on renal physiology in advancing age by Davies and Shock [11] are of particular interest, for the magnitude of decrease in renal plasma flow (53%) and glomerular filtration rate (46%) is much greater than occurs in the cerebral circulation. Further studies on renal hemodynamics have indicated that after administration of a standardized pyrogen there is a uniform increase in renal blood flow in all age groups.[14] In both brain and kidney, then, the increased vascular resistance of age is not fixed.

One might postulate that the data reported here make the frequency of cerebral vascular thrombosis in the elderly more understandable. In the presence of an already compromised cerebral circulation and metabolism, the occurrence of any untoward physiological phenomenon, such as transitory hypotension, might result in sufficient further reduction of cerebral blood flow to encourage stasis and intravascular clotting. The frequent occurrence of areas of encephalomalacia without demonstrable blood-vessel clotting on pathological examination may conceivably be explained by a reduction in cerebral metabolism in that area to a level incapable of maintaining cell viability, without actual vascular thrombosis occurring.

It is surprising to note that the mean values for cerebral blood flow and metabolism in this group of normal subjects aged from 38 to 79 were similar to those obtained in a group of patients of about the same average age but with known clinical evidence of cerebral vascular disease without alteration in mental status.[15]

9. Himwich, H. E.: Brain Metabolism and Cerebral Disorders, Baltimore, Williams & Wilkins Company, 1951.

10. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Ed. 2, Vol. 1: Methodology and Controls, Cambridge, Mass., Addison-Wesley Press, Inc., 1951.

11. Davies, D. F., and Shock, N. W.: Age Changes in Glomerular Filtration Rate, Effective Renal Plasma Flow, and Tubular Excretory Capacity in Adult Males, J. Clin. Invest. **29**:496, 1950.

12. Lewis, W. H., Jr.: Changes with Age in the Cardiac Output in Adult Men, Am. J. Physiol. **121**:517, 1938.

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15. Scheinberg, P.: Cerebral Blood Flow in Vascular Disease of the Brain with Observations on the Effects of Stellate Ganglion Block, Am. J. Med. **8**:139, 1950.

It would seem that normal middle-aged subjects differ from those with clinical evidence of cerebral vascular disease only in the degree of severity of the disease and in the chance location of an atheromatous or occlusive lesion, with resulting neurologic symptoms. This concept has previously been expressed by Gould with relation to vascular disease generally.[16]

The data here presented indicate the necessity for using control subjects of comparable age group in making physiologic observations on cerebral circulation and metabolism in various disease states. Indeed, one might question whether it is possible to consider subjects in an elderly age group as "normal," despite lack of clinical evidence to the contrary, since physiologic evidence of cerebral vascular and metabolic impairment is present.

SUMMARY

Cerebral blood flow and metabolism were measured by the nitrous oxide method in 32 normal men between the ages of 38 and 79 years and the data compared with those obtained in previous similar studies on 19 normal subjects between the ages of 18 and 36 years.

There is a close statistical correlation between advancing age and decreasing cerebral blood flow and increasing cerebral vascular resistance. The reduction in cerebral blood flow and increase in cerebral vascular resistance are accelerated after middle age. Cerebral oxygen consumption remains fairly stable until after middle age, when it apparently begins to decrease with advancing age.

The reduction in cerebral blood flow and increase in cerebral vascular resistance are thought to be due to increased cerebral vascular tone and vascular sclerosis. Diminution in cerebral oxygen consumption is thought to result from impaired cellular function resulting from reduced blood flow.

In eight of the subjects inhalation of a mixture of 10% CO_2 and 90% O_2 resulted in apparent increases in cerebral blood flow of more than 100%; indicating that the increased cerebral vascular resistance of the aged is not necessarily fixed.

Mrs. Janet Fetner gave technical assistance.

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CENTRAL NEUROLOGICAL COMPLICATIONS OF HYPOPARATHYROIDISM

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IT IS WELL known that calcium ions are necessary for the proper functioning of nerve tissue. Lack of calcium ion increases the excitability of nerve tissue to the point that, in vitro, mammalian A fibers will discharge spontaneously in the presence of low calcium (Kugelberg,[1] 1944). Arvanitaki[2] (1942) was able to create an artificial synapse ("ephapse") by allowing nerve fibers to cross one another: In the presence of low calcium ions, impulses set up in the receiving fiber were able to initiate propagated responses. The increased neuromuscular irritability in mammals associated with hypocalcemia is commonly termed tetany and is looked for in terms of carpopedal spasm, laryngeal stridor, muscular cramps, Chvostek's sign, and changes in electrical excitability of the peripheral nerves. Koenig and associates[3] (1952) have shown by nerve section and use of curare that all the phenomena of tetany can be ascribed to iterative discharges in peripheral motor fibers or their terminations.

Much less well known are the syndromes arising from parathyroid deficiency (and its consequent hypocalcemia) which involve the central nervous system. Lachman[4] (1941) listed "various cerebral and mental disturbances as epileptiform convulsions, changes in character, hallucinations, dementia." A number of other conditions are also associated with hypoparathyroidism (papilledema, pseudotumor cerebri, cerebral calcification, mental deficiency, and extrapyramidal syndromes). The recent observations on some of the effects of hypoparathyroidism on the central nervous system which were confused with other diseases of the nervous system have led to a review of the literature and of cases which have appeared at the Illinois Neuropsychiatric Institute.

The incidence of idiopathic hypoparathyroidism is very low.[5] The occurrence of parathyroid deficiency after thyroidectomy is variously estimated from 4.2 to

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2. Arvanitaki, A.: Effects Evoked in an Axon by the Activity of a Contiguous One, J. Neurophysiol. **5**:89-108, 1942.

3. Koenig, H.; Stahlecker, H., and Koenig, R. S.: The Neuromuscular Mechanisms of Alkalotic and Hypocalcemic Tetany, Proc. Soc. Exper. Biol. & Med. **79**:330-333, 1952.

4. Lachman, A.: Hypoparathyroidism in Denmark: A Clinical Study, Acta med. scandinav. 1941, Supp. 121.

5. Kowallis, in 1941, could find records of only 10 cases of idiopathic hypoparathyroidism at the Mayo Clinic, when he reported the 11th. Wise and Hart (1952) found 3 cases in a 10-year survey at the Kings County Hospital, where the yearly admission rate is 62,000.

0.08%. Gargill and Berlin [6] (1941) found hypoparathyroidism in 14 of 120 patients who had total thyroidectomy for heart disease and in 12 of 500 patients with subtotal excision for toxic or nontoxic goiter. Poer [7] (1941) described the incidence of post-thyroidectomy hypoparathyroidism in a 10-year period as 0.08%. Of 2,000 consecutive cases of thyroidectomy, Bell and Bartels [8] (1951) found postoperative tetany in 2.9%, but permanent tetany (after one to five years) in only 16 (0.8%). It should be added that hypoparathyroidism and hypocalcemia may not be equivalent. Gargill and Berlin observed several patients who after thyroidectomy had paresthesias of the face and extremities, a positive Chvostek sign, and involuntary facial twitching. There were no changes in the levels of blood calcium and phosphorus, but the symptoms were relieved by administration of calcium. Hoesch [9] (1937) believed that hypoparathyroidism could occur without hypocalcemia, especially when there is a familial history, typical cataract, and a good response to dihydrotachysterol (A. T. 10). Lachman [4] suggested that the parathyroids not only regulate blood calcium but also have another function the failure of which gives rise to trophic (and possibly nervous) disturbances. In the case reported by Emerson, Walsh, and Howard [10] (1941) the blood calcium was 10 mg. per 100 cc. in May, and in August it was 5 mg. per 100 cc. Perhaps single determinations of calcium in the blood are not sufficient to establish the diagnosis. The discovery of the syndrome of pseudohypoparathyroidism by Albright, Burnett, Smith, and Parson [11] (1942) has led to the finding that parathyroid hormone may be ineffective in the human and may be replaced by dihydrotachysterol and calcium therapy. In the review and discussions to follow, pseudohypoparathyroidism is considered in the same category as spontaneous hypoparathyroidism and postoperative hypoparathyroidism, for the same metabolic disorders are found and the same therapy is useful.

Although Albright and Reifenstein [12] (1948) stated the belief that the basic metabolic deficit in hypoparathyroidism is failure to excrete phosphorus, evidence presented by Stewart and Bowen [13] (1951) indicates that the parathyroid gland can regulate serum calcium directly (in the absence of the kidneys). For the purposes of this paper, hypocalcemia is considered to be the phenomenon at fault in causing disorders of the peripheral and central nervous system in hypoparathyroidism.

6. Gargill, S. L., and Berlin, D. D.: Postoperative Hypoparathyroidism: Preliminary Report, Tr. Am. A. Study Goiter, 1941, pp. 102-104.

7. Poer, D. H.: Comparison of Results of Treatment of Tetany with Dihydrotachysterol and Vitamin D_2, Tr. Am. A. Study Goiter, 1941, pp. 196-203.

8. Bell, G. O., and Bartels, E. C.: Postoperative Parathyroid Tetany, Lahey Clin. Bull. **7**:105-110, 1951.

9. Hoesch, K.: Katarakt und Nebenschilddrüsenepilepsie, Deutsche med. Wchnschr. **63**: 1582-1585, 1937.

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12. Albright, F., and Reifenstein, E. C., Jr.: The Parathyroid Glands and Metabolic Bone Disease: Selected Studies, Baltimore, Williams and Wilkins Company, 1948.

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EPILEPSY

Mikulicz (1886) and Hoffmann (1888) are said (Gotta [14]) to have been the first to describe the concurrence of epilepsy and tetany in thyroidectomized patients. However, Nathan Weiss, in 1880, described tetanic crises with intermittent episodes of loss of consciousness in a patient from whom a goiter had been removed. In the years which followed, the tentany was shown to be due to parathyroid deficiency, and the relation became one between hypoparathyroidism and epilepsy. Redlich [15] (1911) was able to collect 72 cases of tetany with convulsions; in 22 the disorder could be shown to follow thyroidectomy. Hoesch [9] spoke of observing 50 or 60 patients with tetany, some of whom had migraine, some fainting episodes, and some cataracts. In the differentiation from idiopathic epilepsy, he spoke of looking for evidence of cataract (often by slit-lamp examination), increased excitability of peripheral nerves, and decreased blood calcium. Boothby and Davis [16] (1936) also called attention to cataracts and convulsions in parathyroid insufficiency. Other cases have been reported by Shelling and Goodman [17] (1934), MacBryde [18] (1938, including the same cases as those reported by Barr, MacBryde and Sanders,[19] 1938), Eaton and associates [20] (1939), Drake and associates [21] (1939), Kowallis [22] (1941), McQuarrie and co-workers [23] (1941), Weber and Richardson [24] (1941), Sutphin and associates [25] (1943), Evans and Elliott [26] (1945), Leonard [27] (1945),

14. Gotta, H.: Tetany and Epilepsy, A. M. A. Arch. Neurol. & Psychiat. **66**:714-721, 1951.

15. Redlich, E.: Tetanie und Epilepsie, Monatsschr. Psych. u. Neurol. **30**:439-475, 1911.

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18. MacBryde, C. M.: The Treatment of Parathyroid Tetany with Dihydrotachysterol, J. A. M. A. **111**:304-307, 1938.

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26. Evans, J. A., and Elliott, F. D.: Multiple Vitamin Deficiencies Including Beriberi with Congestive Heart Failure, Lahey Clin. Bull. **4**:173-181, 1945.

27. Leonard, M. F.: Chronic Idiopathic Hypoparathyroidism with Superimposed Addison's Disease in a Child, J. Clin. Endocrinol. **6**:493-506, 1946.

Alexander and Tucker [28] (1949), and Jordan and Kelsall [29] (1951). In Lachman's [4] review of hypoparathyroidism in Denmark, he found seizures in 8 of 56 cases of post-thyroidectomy and in 3 of 22 cases of idiopathic hypoparathyroidism. In recent years, the electroencephalogram has been used in an attempt to determine whether the epilepsy is an incidental disorder or whether it is actually due to hypoparathyroidism. Kowallis [22] found the electroencephalogram showing "atypical cerebral dysrhythmia" in the 32-year-old woman with idiopathic hypoparathyroidoism whose case he reported. With administration of calcium and dihydrotachysterol the record showed "notable improvement." Albright, Burnett, Smith, and Parson [11] reported the first instance of pseudohypoparathyroidism, the condition occurring in a woman with seizures. Her sister and the sister's daughter also had seizures, and the patient's electroencephalogram was abnormal before and after use of dihydrotachysterol and other measures had returned the blood chemistry to normal levels. With normal blood calcium and phosphorus, the patient still had some seizures. Sutphin and associates [25] found a grossly abnormal record without localization in a hypoparathyroid patient with tetany and papilledema; no seizures were reported. Odoriz and co-workers [30] (1944, obtained electroencephalograms on 17 patients with parathyroid deficiency. The records in general showed absence of alpha activity, presence of spikes, and groups of 2 to 3 per second waves. Taubenhaus and Engle [31] (1945) described spiky wave forms and irregular rate and rhythm in their patient with idiopathic tetany and epilepsy; the record was described as showing progressive improvement with calcium therapy. Mortell [32] (1946) found gross dysrhythmia, fast and spike activity, and pronounced hyperventilation response in a girl, aged 19, with idiopathic hypoparathyroidism. After treatment, the electroencephalogram became almost normal, with but a few fast waves in the frontal region and with a few abnormal waves on hyperventilation. According to Fischgold and associates [33] (1948), interseizure records in patients with hypocalcemia are normal. During an episode of spasmodic sobbing in spasmophilia, the electroencephalogram showed changes like those in cortical anoxia or anemia. Gotta and Odoriz [34] (1948) reported on 14 patients with tetany and seizures (in 11 after thyroidectomy). The electroencephalogram showed 2 to 5 per second waves, sometimes with spikes, which were not modified by injections of calcium and were not dependent on the duration of the disease. They concluded that parathyroidism itself did not cause epilepsy but that the lowered calcium levels induced seizures in per-

28. Alexander, S. B., and Tucker, H. St. G., Jr.: Pseudohypoparathyroidism: Report of Case with Late Manifestations, J. Clin. Endocrinol. **9**:862-873, 1949.

29. Jordan, A., and Kelsall, A. R.: Observations on a Case of Idiopathic Hypoparathyroidism, A. M. A. Arch. Int. Med. **87**:242-258, 1951.

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33. Fischgold, H.; Hecaen, H., and Brisac, C.: L'électroencéphagraphie peut-elle preciser les limites de l'épilepsie? Rev. neurol. **80**:274-290, 1948.

34. Gotta, H., and Odoriz, J. B.: The Electroencephalogram in Hypoparathyroidism with Tetany and Epilepsy, J. Clin. Endocrinol. **8**:674-686, 1948.

sons already predisposed to seizures. Abély, Borenstein, and Puech [35] (1950) described seizures in a woman aged 60 who had had thyroidectomy seven years before. The electroencephalogram showed absence of alpha waves, the presence of theta waves, at a frequency of 5 per second, and 2.5 to 3 per second waves anteriorly. After calcium and intraspinal oxygen therapy, the electroencephalogram was normal, with a few 6 per second waves and slight slowing on hyperventilation. Moehlig and Gerisch [36] (1950) found an electroencephalogram "typical of convulsive disorder" in a case in which seizures antedated the discovery of hypocalcemia resistant to parathyroid hormone (hence "pseudohypoparathyroidism"). The patient did improve with calcium therapy. On the basis of repeated records before and after treatment in six cases of epilepsy and postoperative or idiopathic hypoparathyroidism, Gotta [14] concluded that parathyroid insufficiency is a causal factor in epileptic seizures. In his experience, tetany always appeared before epilepsy when the two were coexistent, and the epileptic fits disappeared when the tetany was controlled. Diphenylhydantoin and phenobarbital did not control the seizures in the patient reported on by Schottstaedt and Gordan [37] (1951), whose electroencephalogram showed generalized and focal abnormalities of nonspecific, as well as paroxysmal, nature. There was a focus of abnormality in the right frontal and temporal areas. After cataracts had developed and the diagnosis of idiopathic hypoparathyroidism had been confirmed by laboratory tests, intravenous injection of calcium failed to alter the electroencephalographic abnormalities. Even when proper therapy had brought the blood chemistry to normal and there were no more seizures (even without anticonvulsants), the electroencephalogram remained unchanged. Berardinelli [38] (1951) reported another case of pseudohypoparathyroidism with epilepsy. The electroencephalogram was abnormal, with bursts of slow waves. Simpson [39] (1952) reported that most of the abnormalities in a predominantly 3 to 4 cps record of a boy aged 9 years with idiopathic hypoparathyroidism disappeared after treatment. Later records showed 8 to 9 per second waves, with only some slowing. In a second patient, with idiopathic hypoparathyroidism without epilepsy, the electroencephalogram was interpreted as showing a mild, nonspecific dysrhythmia. Wise and Hart [40] (1952) obtained an essentially normal electroencephalogram from a man aged 53 with idiopathic hypoparathyroidism when the blood calcium was 6.1 mg. per 100 cc. Their other two patients, who had convulsions, had bursts of slow-wave activity, which were partly eliminated by a term of calcium and dihydrotachysterol therapy. In each patient the convulsions ceased

35. Abély, P.; Borenstein, P., and Puech, J.: Manifestations épileptiques périodiques avec retentissement psychique d'origine parathyréoprive: Intérêt de l'insufflation transrachidienne d'oxygène, Ann. méd.-psychol. **108**:345-349, 1950.

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37. Schottstaedt, E., and Gordan, G. S.: Chronic Idiopathic Hypoparathyroidism Simulating Epilepsy: Report of a Case, California Med. **74**:390-391, 1951.

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40. Wise, B. L., and Hart, J. C.: Idiopathic Hypoparathyroidism and Pseudohypoparathyroidism: Observations on the Electroencephalogram in Hypocalcemia, A. M. A. Arch. Neurol. & Psychiat. **68**:78-93, 1952.

with return of the blood calcium to normal. The mechanism of production of epilepsy in hypoparathyroidism is still unknown. Since most patients with hypocalcemia and tetany do not have epilepsy, a constitutional factor must be present. One of the patients whose case was reported by Gotta and Odoriz [34] had seizures after thyroidectomy. His brother had to be hospitalized because of convulsions, followed by amnesia. Ellis [41] (1928) showed that in experimental hypoparathyroidism the brain contains increased water: The association of water retention with epilepsy is well known and is the basis for the posterior pituitary injection test for evocation of seizures. In Simpson's [39] Case 2 the patient noted excess fatigue, muscular weakness, and stiffness of the hands at her menstrual periods. On the other hand, McQuarrie and associates [23] were of the opinion that the increased incidence of seizures with tetany was due not to increased water but to an associated disturbance in surface function of brain-cell membranes, which permits the building up of abnormal electric potentials. The ability of calcium ions to stabilize nerve-cell membranes has been attested by Lorente de Nó [42] (1947): Perhaps the membrane changes which permit accumulation of water are due to loss of calcium ions. Tschirgi [43] (1952), who believed that the perivascular glial membrane is probably the blood-brain barrier, stated: "Thus the threshold of neurones might be, in part, determined by the admission or exclusion of, say, calcium or potassium ions to their environment."

MENTAL CHANGES

In 1907, Frankl-Hochwart pointed out that of 528 patients with tetany, 340 were shoemakers or tailors. He assumed that occupations such as these required no rapid thinking and were all that were available to patients with tetany, who do show mental changes. According to Greene and Swanson [44] (1941), it has been known since 1852 that psychosis may occur with tetany. Redlich [15] described confusion, excitation, and episodes of crying in a woman aged 54 who had had an operation for goiter 12 years before and who had had seizures for 10 years. Barr and associates [19] noted mental retardation and evidence of mental deterioration in a woman aged 21 who had had onset of symptoms of idiopathic hypoparathyroidism at the age of 14. Intelligence quotients of 73 in a boy of 13½ years and of 42 in a girl of 2½ years were found in the hypocalcemic patients with symmetrical calcifications of the basal ganglia. The authors refer to Simon's [45] (1872) statement that mental deficiency and convulsions are often associated with symmetrical brain calcifications. Some, at least, of these patients must have had hypocalcemia. Knospe [46] (1938) reported two cases of psychosis associated with hypocalcemia

41. Ellis, M. M.: Guanidine Studies: III. Water Content of Certain Tissues During Acute Guanidine and Parathyroprivia Tetanies, Biochem. J. **22**:937-940, 1928.

42. Lorente de Nó, R.: A Study of Nerve Physiology, New York, Rockefeller Institute for Medical Research, Vol. 132, pp. 1-548.

43. Tschirgi, R. D.: The Biology of Mental Health and Disease, New York, Paul B. Hoeber, Inc., 1952, chap. 4, pp. 34-36.

44. Greene, J. A., and Swanson, L. W.: Psychosis in Hypoparathyroidism, with a Report of 5 Cases, Ann. Int. Med. **14**:1233-1236, 1941.

45. Simon, T.: Ausgedehnte Verkalkung der Hirngefasse bei einer Idioten, Arch. path. Anat. **55**:534-536, 1872.

46. Knospe, H.: Zwei Fälle von Psychose bei Tetanie, Monatsschr. Psychiat. u. Neurol. **99**:503-520, 1938.

and improvement under treatment with dihydrotachysterol. In 5 of 18 patients with hypoparathyroidism studied by Greene and Swanson [44] psychosis developed. The most usual form is toxic delirium. It is not necessarily related to tetany and convulsions. It improves with return to normal calcium levels, but may recur with hypercalcemia. The psychotic changes are hence attributed to a failure of the cerebrum to adjust to acute chemical changes. Emerson and associates [19] described periodic depressions in a teacher with periodic hypocalcemia: Richter and co-workers [47] (1940) investigated this patient's mood swings more carefully and pointed out that she had cycles of 40 days, with changes from slowed mentality, low spirits, and irritability to a normal state, in the middle of the cycle. The calcium levels varied with these mood changes. The cycles disappeared with proper calcium therapy. Cycles of variation in calcium intake were found by these workers in parathyroidectomized monekeys allowed to take calcium lactate solution or water as they chose. Cantor and Scott [48] (1942) reported an episode of acute confusional psychosis in a woman aged 43 with chronic idiopathic hypoparathyroidism. Remission of the psychosis of the patient aged 43, described by Sevringhaus and St. John,[49] occurred when ergosterol and calcium were given to combat the tetany which had followed thyroidectomy, nine years before.

Two of the patients with hypocalcemia and hyperphosphatemia due to pseudohypoparathyroidism, whose cases introduced this syndrome (Albright, Burnett, Smith, and Parson [11]), were mentally retarded.

Delusions, hallucinations, drowsiness, depression, and intermittent episodes of excitement and irritability cleared with administration of calcium and parathyroid hormone in the case of postoperative hypoparathyroidism reported by Scarlett and Houghtling [50] (1944). Mental dullness improved, and there was increased alertness following calcium therapy in the case of idiopathic hypoparathyroidism recorded by Evans and Elliott. Mortell's [32] patient, a girl, showed a progressive personality change; she was nervous, irritable, short-tempered, demanding, and childish. Psychiatric examination indicated an impairment of sensorium suggestive of organic brain disease, confirmed by psychologic tests. The intelligence quotient was 70. Although a notable improvement in the abnormal electroencephalogram followed administration of calcium, there was no basic change in the psychologic or psychiatric findings. It was concluded that there had been irreversible organic damage to the brain. In discussing the treatment of hypocalcemic cataract, Weekers [51] (1946) referred to a patient with hypocalcemia who was stuporous, and to another who had hydrocephalus and retarded development, with numerous epileptic attacks. Case 8 of Gotta and Odoriz [34] was that of a woman aged 35 in whom manic psychosis, with delusions of persecution and episodes of confusion, developed four

47. Richter, C. P.; Honeyman, W., and Hunter, H.: Behaviour and Mood Cycles Apparently Related to Parathyroid Deficiency, J. Neurol. & Psychiat. **3**:19-26, 1940.

48. Cantor, M. M., and Scott, J. W.: Chronic Idiopathic Hypoparathyroidism, Canad. M. A. J. **47**:551-552, 1942.

49. Sevringhaus, E. L., and St. John, R.: Parathyroid Tetany Treated with Massive Doses of Vitamin D, J. Clin. Endocrinol. **3**:635-637, 1943.

50. Scarlett, E. P., and Houghtling, W. J.: Psychosis in Hypoparathyroidism, Canad. M. A. J. **50**:351-352, 1944.

51. Weekers, R.: Les cataractes par hypocalcémie et leur traitement médicamenteux, Ophthalmologica **107**:256-281, 1944.

years after thyroidectomy and immediate postoperative tetany. Gsell's [52] (1950) patient had psychic changes comparable to those of an organic psychosis. In school, he had gone only to the fourth grade (he had had tetany since childhood). Abely and associates [35] described psychic excitation, confusion, hallucinations, agitation, insomnia, and behavior disturbances in a woman aged 60, who was found to have a thyroidectomy scar. Three years before, she had a confusional, oneiric state after a series of seizures. With calcium and intraspinal oxygen therapy the patient's condition improved. Confusion, disturbed affect, a tendency to laugh and cry without reason, and poor memory were reported in the case of Schottstaedt and Gordan.[37] After proper treatment, the woman was said to be more stable emotionally, and her memory greatly improved. Simpson [39] reported two cases of idiopathic hypoparathyroidism: In one, that of a child of 9 years, the mental age was 4 and the intelligence quotient 48; in the other, that of an adult, a "nervous breakdown" had occurred at 28; at that time there were generalized headaches and attacks of stiffness in both hands, in addition to generalized tiredness. She recovered in about six months and was well until onset of cataract at the age of 43. Later investigation showed idiopathic hypoparathyroidism. The third patient of Wise and Hart [49] had an intelligence quotient (Wechsler-Bellevue Scale) of 57 and was considered emotionally, as well as intellectually, immature.

The mental changes with hypoparathyroidism might be attributed to increased intracranial pressure, but the latter was not a constant finding in these patients. The occasional improvement in psychotic behavior with calcium therapy would lead to the belief that the ionic disequilibrium which in the peripheral nerve is responsible for tetany may, in the central nervous system, lead to mental changes, much as any chemical poisoning may produce toxic psychosis, varying according to the duration and extent of malfunction and the underlying personality structure of the patient.

CEREBRAL EDEMA AND PAPILLEDEMA

Kurt Albrecht [53] (1924) drew attention to the coincidence of papilledema and hypoparathyroid tetany. He reviewed 10 cases reported by earlier writers and added 1 of his own, that of a girl aged 10 years, with symptoms of raised intracranial pressure, low serum calcium, and papilledema. The swelling of the disks and the cerebrospinal fluid pressure gradually returned to normal with oral administration of calcium lactate solution. Shelling and Goodman [17] found bilateral choked disk, muscle spasms, and Chvostek and Trousseau signs in a woman aged 32 who had had thyroidectomy at 20, with postoperative tetany. Grand mal seizures started at the age of 26. The blood calcium was 6.3 mg. per 100 cc., and the phosphorus, 6.4 mg. per 100 cc. She was considered to have parathyroid deficiency and epilepsy, and her condition was improved by a low phosphorus-high calcium diet, with later addition of magnesium. Guillain and associates [54] (1936) noted cerebrospinal fluid

52. Gsell, O.: Chronische idiopathische Tetanie (mit Psoriasis) (hypoparathyreoider Kretinismus), Deutsche. med. Wchnschr. **75**:1117-1121, 1950.

53. Albrecht, K.: Stauungspapille bei Tetanie, Monatsschr. Psychiat. u. Neurol. **55**:55-62, 1924.

54. Guillain, G.; Bertrand, I., and Rouquès, L.: Sur une affection dégénérative spéciale pallido-dentelée se traduisant cliniquement par des phénomènes d'excitation motrice et d'hyperexcitabilité neuro-musculaire et un syndrome hypertensif terminal, Rev. neurol. **65**:737-755, 1936.

pressure of 280 mm. of water in a child of 15 with papilledema, associated with episodes of carpopedal spasm and the Chvostek and Trousseau phenomena. The blood calcium level was 9 mg. per 100 cc. Ventricular tap revealed normal fluid, and a decompression was done. The patient died. Autopsy revealed the parathyroids to be present, but there were concretions in the basal ganglia. The cause of the papilledema and signs of tetany is unclear. Barr, MacBryde, and Sanders [19] described seizures, bilateral cataract, and choked disks in a woman aged 56 who had had thyroidectomy 14 years before. With dihydrotachysterol and calcium the papilledema subsided. In a woman aged 21, with idiopathic hypoparathyroidism, seizures and tetany were not controlled with calcium and viosterol. She was mentally retarded and deteriorated, had lenticular opacities, and choked disks of 3 D., and lumbar puncture revealed a pressure of 350 mm. of water. A brain tumor was suspected. With dihydrotachysterol and calcium therapy, the seizures stopped, the spinal fluid pressure dropped to 175 mm. of water, and the papilledema subsided. Hurxthal [55] (1942) found definite papilledema in a patient after thyroidectomy, with a blood calcium level of 5.7 mg. and a phosphorus level of 5.8 mg., per 100 cc. With use of calcium and viosterol, the calcium rose to 10 mg. and the phosphorus dropped to 4 mg., per 100 cc. Tetany vanished. The papilledema persisted; so a subtemporal decompression was done, with release of a large amount of subdural fluid. For two years the fundi were not normal, and the decompression area varied considerably; thereafter, the decompression area was soft, and the fundi became normal.

Sutphin and associates [25] described papilledema and seizures in a boy aged 12, whose lumbar puncture pressure was 250 mm. of water. Air studies revealed a normal condition. A strongly positive Chvostek sign led to calcium determinations: Calcium was 4.7 mg., and phosphorus 9.3 mg., per 100 cc. With dihydrotachysterol therapy, his alertness returned, the seizures disappeared, and lumbar fluid pressure was normal in 13 days. On reexamination, in five months, there was no more papilledema.

Idiopathic hypoparathyroidism was the diagnosis in the case reported by Evans and Elliott.[26] The patient, a man aged 43, had bilateral cataract removed at the age of 35. Ataxia, tremor, and blurred disks developed. The blood calcium level was 4.1 mg., and the phosphorus level, 7 mg. per 100 cc. Cerebrospinal fluid pressure was 320 mm. Cord bladder developed. When the calcium dropped to 3.6 mg. per 100 cc., he had convulsions. With administration of dihydrotachysterol, vitamin B, and ascorbic acid, the cord bladder disappeared, the optic nerves became normal, and he became alert.

In 1946, Leonard [27] reported the coexistence of hypocalcemia and papilledema, of 3 to 4 D., with normal cerebrospinal fluid pressure in a girl aged 9½ years. The papilledema gradually subsided on calcium and parathyroid hormone treatment. In Mortell's [42] case the cerebrospinal fluid pressure was 240 mm. of water. This dropped to 190 mm. after 10 days of treatment of idiopathic hypoparathyroidism with vitamin D and calcium chloride. Lyle [56] (1947) collected the reports of

55. Hurxthal, L. M.: Increased Intracranial Pressure Associated with Chronic Parathyroid Tetany, Lahey Clin. Bull. **2**:238-242, 1942.

56. Lyle, D. J.: The Ocular Syndrome of Cataract and Papilledema in the Manifest Form of Parathyroid Deficiency, Tr. Am. Ophth. Soc. **45**:101-112, 1947.

papilledema associated with parathyroid deficiency and added what he believed to be the 21st case. The woman, aged 53, had the onset of cataracts, epileptic seizures, and papilledema after thyroidectomy. Lumbar puncture showed a pressure of 200 mm. of water. Within a few days after institution of dihydrotachysterol and calcium lactate therapy the pressure dropped and the papilledema subsided. Levy [57] (1947) reported papilledema in a post-thyroidectomy patient with hypoparathyroidism. This case is included in the present series. Papilledema was found at the initial examination of a 24-year-old patient with hypocalcemic convulsions and bilateral cerebral calcification, whose case was reported by Wise and Hart.[10]

CEREBRAL CALCIFICATION

Calcium was found in the brain and properly identified as early as 1855 and 1856 (see Camp,[58] 1947, for bibliography). The association of brain calcification, tetany, and cataract was pointed out by Pick [59] (1902). Fahr [60] (1930) described "idiopathic nonarteriosclerotic intracerebral vascular calcification" but did not associate it with calcium deficiency disease. His patient did have attacks of "obstetrician's hand" (carpal spasm). Fritsche [61] (1935) was the first to describe roentgenologic evidence of symmetrical calcifications of the brain; no relation to tetany, cataract, or hypocalcemia could be found. Kasanin and Crank [62] (1935) also reported such a case, but no study of the blood calcium was made. Love, Camp, and Eaton [63] (1938) made a preliminary report on six patients with symmetrical cerebral calcification, demonstrable roentgenologically. Eaton and Haines [29] pointed out that three of eight patients with such calcifications had chronic parathyroid insufficiency. This was apparently the first time the association had been made. Eaton, Camp, and Love [64] (1939) gave details from the records of these patients, including the first, who had convulsions, cataract, showed mental reactions, loss of hair, and papilledema; a single blood calcium determination, made elsewhere, gave 11 mg. per 100 cc. Autopsy (death followed air study and exploration) showed globules, fused masses, and mulberry-shaped concrements of calcium. These were around the capillaries, and some were apparently free in the tissues. The largest

57. Levy, H. A.: Unusual Clinical Manifestations of Chronic Hypoparathyroidism, M. Clin. North America **31**:243-253, 1947.

58. Camp, J. D.: Symmetrical Calcification of the Cerebral Basal Ganglia: Its Roentgenologic Significance in the Diagnosis of Parathyroid Insufficiency, Radiology, **49**:568-577, 1947.

59. Pick, A.: Vorläufige Mittheilung zur Pathologie der Tetanie, Neurol. Centralbl. **21**: 578-579, 1902.

60. Fahr, T.: Idiopathische Verkalkung der Hirngefässe, Zentralbl. allg. Path. **50**:129-133, 1930.

61. Fritsche, R.: Eine familiär auftretende Form von Oligophrenie mit röntgenologisch nachweisbaren symmetrischen Kalkablagerung im Gehirn, besonders in den Stammganglien, Schweiz. Arch. Neurol. u. Psychiat. **35**:1-29, 1935.

62. Kasanin, J., and Crank, R. P.: A Case of Extensive Calcification in the Brain: Selective Calcification of the Finer Cerebral Blood Vessels, Arch. Neurol. & Psychiat. **34**:165-178, 1935.

63. Love, J. G.; Camp, J. D., and Eaton, L. M.: Symmetrical Cerebral Calcification, Particularly of the Basal Ganglia, Demonstrable Roentgenologically, Associated with Cyst of the Cavum Septi Pellucidi and Cavum Vergae, Proc. Staff Meet., Mayo Clin. **13**:225-232, 1938.

64. Eaton, L. M.; Camp, J. D., and Love, J. G.: Symmetric Cerebral Calcification, Particularly of the Basal Ganglia, Demonstrable Roentgenographically: Calcification of the Finer Cerebral Blood Vessels, Arch. Neurol. & Psychiat. **41**:921-942, 1939.

were in the globus pallidus; then in the putamen, thalamic and caudate nuclei, and dentate nuclei, with slighter changes in the red nucleus, substantia nigra, pontine reticular substance, and the gray and white matter of the cerebrum and cerebellum. No changes were found in the cornu ammonis, the mamillary or olivary bodies, or the spinal cord. Eaton and Haines[49] added the seventh reported case of parathyroid insufficiency and bilateral symmetrical calcification, in which there had been seizures, impaired memory, mental retardation, and cataracts. Vasiliu[65] (1940) found hypoparathyroidism in three of six patients whose roentgenograms of the skull showed symmetrical calcifications. The location of the deposits in the heads of the caudate nuclei was made more certain by pneumoencephalography. Others reporting cases of cerebral calcification with hypoparathyroidism were Sevringhaus,[66] Sprague[67] (1945), and Siglin[68] (1947), Siglin being the first to show such roentgenologic changes after thyroidectomy; in all the others the condition had been due to idiopathic hypoparathyroidism. Lowenthal[69] (1948) reviewed the reports in the literature of 32 cases of Fahr's bilateral symmetrical calcification syndrome, 23 of which were verified by necropsy and 13 by x-rays. Chemical or clinical evidence of hypocalcemia and tetany was found in 13 cases. The status of the calcium metabolism in the case of Chavany, van Bogaert, and Houdart[70] (1949) and in that of Környey and Máttyus[70a] is unknown. The case reported by Alexander and Tucker[28] was apparently the first of bilateral calcification in which hypocalcemia did not respond to parathyroid hormone, and hence a diagnosis of pseudohypoparathyroidism was made. Another such case was reported by Bishop and DeMowbray[71] (1951). Jordan and Kelsall[29] found bilateral mottled calcification in the frontal areas, cylindrically arranged along the ventricles, in a case of idiopathic hypoparathyroidism. Medill[72] (1951) reported another case of calcification of the basal ganglia associated with hypoparathyroidism. Berardinelli's[38] patient had x-ray evidence of calcification in the right superior parietal region.

The significance of density in the x-rays of the skull in the case of epilepsy reported by Schottstaedt and Gordan[37] was apparently missed; since the patient

65. Vasiliu, D. O.: Sechs Fälle von symmetrischer intrazerebraler Kalkablagerung in den Stammganglien, verbunden mit epileptischen Anfällen und Geistesstörung, diagnoziert mit Hilfe der Kraniographie und Encephalographie, Wien. med. Wchnschr. **11**:153-157, 1940.

66. Sevringhaus, E. L.: Activated Sterols and Calcium Salts in the Treatment of Parathyroid Tetany, Am. J. M. Sc. **203**:726-731, 1942.

67. Sprague, R. G.; Haines, S. F., and Power, M. H.: Metabolic Effects of Parathyroid Hormone, Dihydrotachysterol and Calciferol in Case of Pseudohypoparathyroidism, J. Lab. & Clin. Med. **30**:363-364, 1945.

68. Siglin, I. S.; Eaton, L. M.; Camp, J. D., and Haines, S. F.: Symmetric Cerebral Calcification Which Followed Postoperative Parathyroid Insufficiency: Report of a Case, J. Clin. Endocrinol. **7**:433-437, 1947.

69. Löwenthal, A.: La calcification vasculaire intracérébrale non artériosclércuse de Fahr est-elle la manifestation cérébrale d'une perturbation des fonctions parathyroïdiennes? Acta neurol. et psychiat. belg. **48**:613-631, 1948.

70. Chavany, J. A.; van Bogaert, L., and Houdart, R.: XIII. Aspects extrapyramidaux de la "calcification vasculaire intracérébrale non arteriosclereuse idiopathique" de Fahr, Monatsschr. Psychiat. u. Neurol. **117**:77-97, 1949.

70a. Környey, S., and Máttyus, A.: Zur Kenntnis der vornehmlich striato-dental lokalisierten Kalkablagerung im Gehirn, Monatsschr. Psychiat. u. Neurol. **119**:1-24, 1950.

71. Bishop, P. N. F., and DeMowbray, R. R.: Pseudohypoparathyroidism, Proc. Roy. Soc. Med. **44**:952-954, 1951.

72. Medill, E. V.: Bilateral Symmetrical Calcification of the Basal Ganglia Associated with Parathyroid Insuficiency, Brit. J. Radiol. **24**:685-688, 1951.

was 37 when her seizures started, a pneumoencephalogram was made. It was normal. When cataracts formed and the diagnosis was made, the pneumoencephalographic study was repeated. In addition to the calcification of the basal ganglia there was some calcium in the left anterior fossa. "Retiform, worm-like conglomeration of calcific densities in the midportion of the brain substance to either side of the midline" was reported in the roentgenogram of the skull in the third case of hypoparathyroidism reported by Wise and Hart.[40]

The mechanism of the calcification is uncertain. Schiele [73] (1931) considered the substrate to be any pathologic disease of the brain (primary or secondary to a systemic disorder) in which there is a precipitation of pseudocalcium in the perivascular lymph spaces of the brain. This material is a colloid of protein nature and may be derived from sick and dead ganglion cells. According to Schiele, these deposits delay the absorption of lymph and hence cause damage to the blood vessel walls, which leads to calcification. Volland [74] pointed out the resemblance of the deposits to those of Sturge-Weber disease, in which there is also postulated a localized change in cerebral metabolism. Why the disorder should affect primarily the extrapyramidal ganglia is unknown.

Evans and associates [75] (1940) reported two cases of cerebellar calcification, presumably following partial occlusion of cerebellar vessels. Calcium was found deposited on walls of larger arterioles, and local calcospherites, as a result of deposition in smaller, later obliterated, vessels, were observed. The deposition was attributed to the formation of insoluble calcium salts, due to interference with local tissue respiration. Albright and Reifenstein [12] attributed the deposits of calcium in hypoparathyroidism to local increases in phosphate ion, perhaps the result of the splitting of this ion from organic phosphates. Calcification was found more commonly in soft tissues in pseudohypoparathyroidism than in true hypoparathyroidism. The symmetrical calcification in the basal ganglia was considered evidence of supersaturation with calcium phosphate in these regions. Löwenthal [69] reviewed the literature on the histochemistry of intracerebral vascular calcification and concluded that the basic deposit was one of organic protein, not amyloid, containing calcium and sometimes iron. The pseudocalcification of histologists he considered to be the residue of this deposit when the calcium has been leached out by formol fixation. He was unable to affirm or deny the presence of a local metabolic disturbance which might account of the deposition of the protein and calcium. Környey and Mättyus [76a] considered the sequence to be that of disordered brain metabolism, followed by precipitation of colloidal organic substances, which are imbibed secondarily by mineral salts.

73. Schiele, B. G.: Über vorwiegend perivasale, sekundär verkalkende Konkrementbildung im Hirngewebe, Virchows Arch. path. Anat. **282**:790-820, 1931.

74. Volland, W.: Über intracerebrale Gefässverkalkungen: Die idiopathische Form mit vorwiegend extrapyramidalen Krankheitsbild, nebst Bemerkungen zur Sturge-Weberschen Krankheit, Arch. Psychiat. **111**:5-47, 1940.

75. Evans, H. S.; Friedman, A. P., and Courville, C. B.: Calcification of Small Vessels of Cerebellum: Report of 2 Cases with Traumatic Cerebellar Hemorrhages, Bull. Los. Angeles Neurol. Soc. **5**:18-30, 1940.

76. Footnote deleted.

Certainly, intracerebral calcification need not be due to hypoparathyroidism, although many of the reported cases lack data on calcium levels (e. g., Bassoe and Hassin,[77] 1921). In two of the five members of the family with calcification of vessels described by Geyelin and Penfield[78] (1929) the blood calcium levels were normal. In the case of Guillain and associates[64] the calcium level was 9 mg. per 100 cc., but the patient had tetany, convulsions, and papilledema; calcium produced some improvement. At autopsy the parathyroids were found to be normal. Iron, calcium, and colloid deposits were found in the pallidum and dentate nuclei. Other cases have been reported (Volland,[74] Kasanin and Crank,[62] Chavany and associates,[70] Kornyey and Máttyus, [70a] and Mulder and Denst[79]), without studies on blood calcium.

CEREBROSPINAL FLUID FINDINGS

The concentration of calcium in the cerebrospinal fluid is variously reported to be 4.5 to 5.5 mg. per 100 cc. (Michaels[80]) or 4 to 5 mg. per 100 cc. (Barr and associates[19]). Certainly, the level in hypoparathyroidism does not parallel that of the blood. Barr and associates[19] found the spinal fluid calcium to be 5.1 mg. per 100 cc. and the phosphorus 1.9 mg. per 100 cc. in a patient whose blood contained 6.4 and 6.8 mg., per 100 cc., respectively. McQuarrie and associates[23] found 3.9 mg. of calcium and 2.6 mg. of phosphorus per 100 cc. of spinal fluid in a boy whose blood calcium was 6.8 mg. and blood phosphorus 7.6 mg. per 100 cc. Wise and Hart's second patient had 5.4 mg. of calcium per 100 cc. of cerebrospinal fluid when the blood had 6.1 mg. per 100 cc. On the other hand, Kasanin and Crank reported a spinal fluid calcium level of 9.4 mg. per 100 cc. in their patient with bilateral symmetrical calcifications; unfortunately, a blood calcium determination was not done.

OTHER NEUROLOGICAL MANIFESTATIONS

A wide variety of clinical syndromes has been associated with cerebral calcification (e. g., Fritsche[61]; Volland[74]), but these may merely be an expression of the basic cerebral damage which has led to the calcification. However, some are apparently associated primarily with calcium deficiency. Evans and Elliott[20] reported development of "cord bladder" in a patient with idiopathic hypoparathyroidism whose blood calcium level was 4.1 mg. per 100 cc., with a phosphorus level of 7 mg. per 100 cc. There were also ataxia in both legs, increased deep reflexes in the left arm, absence of abdominal reflexes, and tremor of the hand, lip, and tongue. With dihydrotachysterol, vitamin B, and ascorbic acid, the neurologic symptoms disappeared. A case of extrapyramidal syndrome was reported by Chavany and associates,[70] and another by Kornyey and Máttyus,[70a] but in neither case was the blood calcium studied. Simpson[39] reported choreiform movements in a case of idiopathic hypoparathyroidism. Polydipsia and polyuria were found in the girl with pseudohypoparathyroidism whose case was reported by Berardinelli.[38]

77. Bassoe, P., and Hassin, G. B.: Calcification of the Cerebral Vessels with a Clinical Picture Simulating Brain Tumor, Arch. Neurol. & Psychiat. **6**:359-376, 1921.

78. Geyelin, H. R., and Penfield, W.: Cerebral Calcification Epilepsy: Endarteritis Calcificans Cerebri, Arch. Neurol. & Psychiat. **21**:1020-1043, 1929.

79. Mulder, D. W., and Denst, J.: Intracerebral Vascular Pseudocalcification Associated with Schizophrenia: Report of a Fatal Case, Dis. Nerv. System **11**:362-366, 1950.

80. Michaels, J. J.: Neuropsychiatric Aspects of Calcium as Viewed from the Different Levels of the Personality: Review of the Literature, Arch. Neurol. & Psychiat. **34**:362-389, 1935

COMMENT

Relation of Central Neurological Changes to Genesis of Hypocalcemia and Hypoparathyroidism.—The foregoing material has emphasized changes in the central nervous system and its function due to the hypocalcemia and hyperphosphatemia caused by hypoparathyroidsm. The converse has also been suggested, namely, that lesions of the brain may cause hypoparathyroidism.

In 1940 Scheinker [81] attributed tetanic spasms to a release mechanism produced by damage to the pallidodentate "system," for he found fine and dense calcifications around the blood vessels of these regions in a patient with tetany. Richter and associates [47] found 40-day cyclic variations in blood calcium levels in parathyroidectomized monkeys, indicating that a factor other than the parathyroid glands affected the mineral metabolism.

Winer [82] reported a case in which diffuse encephalopathy of traumatic origin was assumed to be responsible for typical hypoparathyroidism. Dilation of the third ventricle was interpreted as compatible with hypothalamic injury. Subsequent premature ejaculation and impotence were considered to affirm the hypothalamic dysfunction.

Since a pneumoencephalogram taken soon after onset of seizures, at the age of 37, was normal, and Chvostek's sign was elicited early, it is more probable that the hypoparathyroidism was unrelated to the injury, and, indeed, that the cerebral changes may have been due to the hypocalcemia of idiopathic hypoparathyroidism. On the other hand, Zondek's [83] (1945) patient had encephalitis lethargica, disturbances of water and salt metabolism, disordered temperature regulation, and considerable variance in blood calcium levels. From this, the author assumed that the tetanic episodes were directly related to a diencephalic lesion of postencephalitic origin. Pette [84] (1949) investigated a number of patients with tetany and normal blood calcium levels who were not benefited by calcium and dihydrotrachysterol therapy. Since these patients improved with sedatives and psychotherapy, he concluded that there was a diencephalic center which had to do with the syndrome of tetany. Hyperventilation produced attacks in these patients, but no information regarding the acid-base balance is available.

Abély and associates [35] employed intraspinal oxygen insufflations in patients with hypoparathyroid tetany and psychosis; they attributed the recovery to the effect of the oxygen on the central mechanisms which they assumed to be responsible for tetany.

REPORT OF CASES

Case 1.—F. A., a married white woman, was first seen in the surgical outpatient department on Jan. 29, 1943, at the age of 36, because of swelling and pain in the neck of two years' duration; she had also had nervousness and difficulty in breathing for two years. The swelling in the neck had increased, and she had been given iodides by her physician but had discontinued

81. Scheinker, I. M.: Tetanie und Zentralnervensystem (zerebraler Auslösungsort tetanischer Krampfmechanismen), Monatsschr. Psychiat. u. Neurol. **103**:44-57, 1940.

82. Winer, N. J.: Hypoparathyroidism of Probable Encephalopathic Origin, J. Clin. Endocrinol. **5**:86-91, 1945.

83. Zondek, H.: Some Observations on the Question of Hypoparathyroidism of Diencephalic Origin, Correspondence, J. Clin. Endocrinol. **5**:431-432, 1945.

84. Pette, H.: Zum Problem der zentralen Genese tetanischer Syndrome, Deutsche Ztschr. Nervenh. **160**:285-298, 1949.

their use recently. Examination showed a somewhat obese white woman with enlargement of both lobes and the isthmus of the thyroid, the gland being palpable down to the sternum. The basal metabolic rate was + 1%. She was hospitalized on May 12, 1943, and the following day a total radical thyroidectomy was done. The operative record stated that portions of the posterior lobe were left on each side, amounting to 1 to 2 gm. of tissue. Severe parathyroid tetany developed on the second postoperative day. She was put on a regimen of high-calcium diet, vitamins, and parathyroid hormone and was discharged on May 19. She received 1 cc. of parathyroid hormone (Parathormone), containing 100 units, on May 26, May 28, and June 1. On the last day the blood calcium content was 6 mg. per 100 cc.; so a capsule of dihydrotachysterol (0.625 mg.) was added. This did not raise the blood calcium level, however; so she was admitted to the medical service on June 4. She complained of weakness, stiffness of movements, cramping of the muscles, nausea, and two episodes of carpopedal spasm. She was obese, with puffy eyes, and positive Chvostek and Trousseau signs. The basal metabolic rate was −24%. The calcium level was 6.8 mg. per 100 cc., with 5.55 mg. of inorganic phosphorus, 4.5 gm. of serum albumin and 2.8 gm. of serum globulin, per 100 cc. She was given 40 gm. of calcium gluconate and three pearls of dihydrotachysterol (Hytakerol), 0.625 mg. each, daily. Her symptoms were promptly improved, but because of constipation the calcium was reduced to 20 gm. a day. At the time of discharge, on June 26, the serum calcium was 8.4 mg., and the phosphorus 4.5 mg., per 100 cc. Reexamination on Aug. 18, because of cramping in the fingers and toes, stiffness of the facial muscles, and twitching around the mouth, disclosed a positive Chvostek sign bilaterally. She was given 1 grain (65 mg.) of thyroid daily, in addition to 3 capsules of dihydrotachysterol and 40 tablets (5 grains [0.30 gm.] each) of calcium gluconate daily. A month later the blood calcium was 6 mg., and the phosphorus 5.3 mg., per 100 cc. She gradually decreased her medication, and when she was seen on May 16, 1945, she complained again of weakness and tingling of muscles. There was evidence of latent tetany but no evidence of cataract. She was again given dihydrotachysterol (1 capsule daily) and 3 tsp. (about 12 gm.) of calcium lactate powder daily. Because of lack of clinical improvement, the dihydrotachysterol was increased to 3 capsules a day, and she was referred to the department of ophthalmology because of blurred vision. Here, no evidence of cataract was noted, but there was bilateral papilledema. She was therefore referred to the department of neurology and neurological surgery, where she was found to have areflexia, a bilateral Chvostek sign, and 3 D. of papilledema. The ocular findings suggested increased intracranial pressure; she was therefore hospitalized on June 18, 1945. At this time she gave a history of headaches and momentary clouding of vision three or four times a day. The headaches were worse at night and involved especially the right side of the head. Lumbar puncture showed a pressure of 215 mm. of water, and the fluid was normal except for a protein content of 48 mg. per 100 cc. X-rays of the skull disclosed an enlarged sella turcica (17 by 18 mm.). The visual fields were normal, with an acuity of 8/10 on the right and of 10/10 on the left. An electroencephalogram, done on June 20, 1945, was reported to show a normal, 10 cps record, without evidence of damage in the accessible cortex (Dr. F. A. Gibbs). Ventriculography was suggested but refused, and the patient left the hospital on June 26, 1945, to return on July 24, 1945. The following day a ventriculographic examination was done, revealing moderately increased intracranial pressure, a normal-appearing parietal cortex, and slight enlargement of the left lateral ventricle. There was no evidence of displacement or deformity of the ventricular system. She was discharged on Aug. 3, 1945, with the idea that a subtemporal decompression might be done if any signs of visual impairment were noted. Examinations in the ophthalmology clinic on Aug. 14, 1946, and as late as Oct. 29, 1947, revealed no change in the disks, normal fields, and sustained good visual acuity. During this time she was seen periodically in the medical clinic; her symptoms of tetany were controlled with 5 capsules (3 mg.) of dihydrotachysterol and 6 gm. of calcium lactate daily and a low-phosphorus diet. In June, 1947, the dihydrotachysterol was increased to 7 pearls (4.1 mg.) a day. In November, 1947, there was still a mild Chvostek sign, but the Sulkowitch test for urinary calcium gave a positive reaction with 7 pearls of dihydrotachysterol and 24 tablets (5 grains [0.30 gm.] each) of calcium lactate daily. In January, 1946, the blood calcium was 6.5 mg., and the phosphorus, 5.2 mg. per 100 cc. In March the levels were 9.0 and 4.7 mg., respectively, but they fell by April, 1947, to 8.1 and 5.2 mg., respectively. Another electroencephalogram, on Nov. 11, 1945, was considered to be a normal

11 cps record, without evidence of localized damage in the cerebral cortex. When she was last seen in the neurology clinic, on Oct. 25, 1945, bilateral papilledema was still present.

From November, 1947, to June 30, 1952, she was under the care of a private physician. She was seen on the latter date, at my request. She had had numerous episodes of carpal and pedal spasms. Intermittent headaches were relieved by taking calcium. She has been capricious in taking medication, and at this time was taking a multiple vitamin preparation, thyroid, cod liver oil, 10 tablets (5 grains each) of calcium lactate, but only 3 capsules of dihydrotachysterol a day. Examination revealed nothing significant except for a bilaterally pronounced Chvostek sign and blurred disk margins (less than 1 D. of elevation) bilaterally. X-rays of the skull showed no changes, with the enlargement of the sella turcica unaltered from that shown in 1945. There was no evidence of bilateral calcifications. The ophthalmologist also reported nasal blurring of the disks (no frank elevation), with no evidence of the cataracts of tetany on slit-lamp examination. The blood calcium level was 6.3 mg., and the phosphorus level 4.8 mg., per 100 cc. The patient has failed to return for further studies.[85]

Case 2.—B. K., a married white woman, was referred to the Illinois Neuropsychiatric Institute from the Illinois Eye and Ear Infirmary because of cataracts and seizures. With the menarche, at the age of 13, seizures had started. In these attacks, an aura of a light, airy sensation and needlelike paresthesias in the left leg was followed by loss of consciousness and a tonic convulsion, with disorientation for several hours. At the age of 19, because of difficulties at home following the birth of her first child, she had a "nervous breakdown," with seizures as often as three times a day (formerly they had been less frequent than once a month). At the age of 21 she had a second "breakdown." At 24, because of nervousness and convulsions, she was sent to the Dixon State Hospital, where she stayed for 14 weeks. She was told her symptoms were due to her "nerves." At 26, after a bout of rheumatic fever, she had another "breakdown," with seizures almost continuously for a week, without awareness of her surroundings. For the two years before her examination she noted that she had increasing difficulty in seeing and that for a few days before and after her menses she would have stiffening in the leg muscles. On examination at the age of 27, on Nov. 10, 1943, she was found to have bilateral cataract, bilateral Chvostek and Trousseau signs, and a moderate increase in all deep reflexes. No abnormal reflexes were seen. The blood calcium level was 4.55 mg., and the blood phosphorus level, 7.30 mg. per 100 cc. An electroencephalogram was reported to indicate cerebral dysrhythmia (no details are available) and the patient was put on calcium phosphate therapy (3 grains [0.20 gm.] three times a day). On Dec. 6, 1943, another electroencephalogram was taken. The occipital areas had 8 per second waves, mixed with some 16 cps, faster activity; 20 to 22 per second waves were found in both frontal and central regions. In March, 1944, polydipsia and polyphagia developed; x-rays of the skull were therefore taken. No abnormalities were seen. The blood calcium remained low (4.0 mg. per 100 cc.), with a high phosphorus level (7.34 mg. per 100 cc.). She was then given 1 cc. of parathyroid hormone (100 units) weekly by intramuscular injection, for five weeks. She was then taken to another hospital, with pneumonia, and was lost sight of until Aug. 22, 1947, when she was admitted to the hospital because of continuing seizures. Examination revealed bilateral cataract and hypotonicity of all the deep reflexes. She was euphoric, slowed in all responses, but cooperative. The following findings (per 100 cc. of blood) were noted: calcium, 5.2 mg.; phosphorus, 8.0 mg.; alkaline phosphatase, 1.7 units; serum proteins, 7.7 gm. (albumin, 4.9 gm.; globulin, 2.8 gm.); carbon-dioxide-combining power, 63 vol. %. An electrocardiogram was interpreted as borderline because of a prolonged Q-T interval, considered diagnostic of hypocalcemia. The ophthalmologist found bilateral anterior cortical cataract and recommended operation when the patient's general condition was improved.

Lumbar puncture was not done. X-rays showed normal structures of the skull but moderate demineralization of the spine. An electroencephalogram, taken on Sept. 12, 1947, showed a normal waking record, but during sleep there were 4 to 6 per second slow waves in the frontal region, with absence of normal 14 per second spindles. She was given diphenylhydantoin (0.1 gm. four times a day) and phenobarbital (0.1 gm. twice daily) for the seizures, placed on a high calcium-

85. Dr. Herman Levy permitted me to use the material of this case report, previously used by him[57] (1947).

low phosphorus diet, and given 100,000 units of vitamin D daily. However, the blood calcium levels remained low; on Sept. 6, 1947, therefore, the patient was put on a regimen of 6 pearls (0.625 mg. each) of dihydrotachysterol and 40 gm. of calcium lactate daily. With this, the Sulkowitch test for urinary calcium excretion became positive. The patient appeared to be somewhat improved, and, since her care appeared to be a long-term matter, she was transferred to the Cook County Hospital on Sept. 20, where an extracapsular lens extraction was done on the right eye. She was discharged on Oct. 6. Four days later, she was admitted to the Elgin State Hospital in a state of intense excitement, appearing acutely ill and with a hacking cough. She employed obscenities, expressed delusions that others had destroyed her baby, and insisted that hospital officials were going to shoot her "between the legs." The initial impression was that of an acute schizophrenic excitement. Examination revealed pupils of 4 mm., which did not react to light, slight slurring of speech, normal deep reflexes, absence of abdominal reflexes, and increased temperature (101.2 F. rectally). The spinal fluid (including pressure) was completely normal. The serum calcium level was 11.5 mg., and the phosphorus 4.1 mg., per 100 cc. About a week later she had a grand mal seizure, after which the mental excitement disappeared. She became irritable, and overly demanding for attention, but was uncooperative and careless in personal hygiene and appearance. There was increased nerve and muscle irritability, manifested by Chvostek and Trousseau signs. With improvement in her physical condition, electric shock treatment was started. After the third treatment, she had a grand mal seizure, followed by a definite carpopedal spasm. Electric shock treatment was then discontinued. Her mental state was considered greatly improved. On Nov. 22, 1947, she was found to be pulseless, with peripheral vascular collapse and the blood pressure unobtainable. A diagnosis of pleural effusion, left side; ascites, and enlargement of the liver was made; 500 cc. of clear, straw-colored fluid was removed from the left pleural cavity (containing no evidence of Mycobacterium tuberculosis, but with a number of white blood cells, 95% of which were lymphocytes). The patient soon went into shock and died. A necropsy was not permitted.

Case 3.—A married white woman aged 33, was referred to the Illinois Neuropsychiatric Institute from the Illinois Eye and Ear Infirmary because of seizures. She had been treated at the Infirmary because of cataracts, which had been known to exist for five years, and the cataract on the left had been removed. She had had a thyroidectomy seven years before for goiter. Ever since, she had had episodes of stiffening without unconsciousness, said to have been tonic seizures. For six years she had had major epileptic attacks, originally only one a year but recently every two or three weeks, usually during sleep. According to her family, these were typical tonic-clonic seizures. Examination revealed the scar of the thyroidectomy, a cataract in the right eye, which prevented visualization of the fundus, and a normal fundus in the left eye. There was a fine tremor of both hands. No deep reflexes were elicitable. The only disturbance of sensation was impairment of perception of figure writing in the right hand. There was a questionable extensor toe sign on the right. Chvostek's sign was readily elicited on both sides, and typical carpal spasm was elicited on hyperventilation. The findings on lumbar puncture and x-ray study of the skull were completely within normal limits. The urine was normal. The blood was normal, with 69 mg. of glucose, 33 mg. of nonprotein nitrogen, and 8 gm. of serum protein (5.9 gm. albumin, 2.1 gm. globulin), per 100 cc.

The electroencephalogram showed 7 to 8 cps activity in all leads, with depression of amplitude in the right temporal and parietal areas. The record was considered to show a moderately abnormal, slow rhythm. The patient was placed on a low-phosphorus diet without milk, and with 40 gm. of calcium lactate daily. Six capsules of dihydrotachysterol (0.625 mg. each) daily were given. Aluminum hydroxide gel U. S. P. (Amphojel), ½ oz. (15 gm.) before each meal, was given to stop the absorption of phosphorus. On the day this treatment was begun, the blood calcium level was 4.9 mg., and the phosphorus level 7.9 mg., per 100 cc., with 2.3 units of alkaline phosphatase. In 10 days the levels were 8.7 mg. of calcium, 6.8 mg. of phosphorus, and 1.6 units of alkaline phosphatase, per 100 cc. Two weeks after the beginning of treatment the calcium was 10.2 mg., with 5.4 mg. of phosphorus and 2.6 units of alkaline phosphatase, per 100 cc. During this period the aluminum hydroxide gel was discontinued, the dihydrotachysterol was decreased to 3 pearls a day, and the calcium lactate, to 20 gm. a day. These changes were dictated by the continued excretion of calcium in the urine, as shown by

the Sulkowitch test. The patient was discharged on July 12, 1947, asymptomatic and taking 2 pearls (1.25 mg.) of dihydrotachysterol and 20 gm. of calcium lactate daily. By October, 1947, she was asymptomatic, on a regimen of only 1 capsule (0.625 mg.) of dihydrotachysterol every other day and only 8 gm. of calcium lactate a day. When she was last seen, on Jan. 16, 1948, she was still free from symptoms, and neither Chvostek nor Trousseau sign could be elicited.

Case 4.—F. W., a white man aged 36, had attacks for about 10 years in which he would stare and mumble, grope, and stiffen the entire body, without convulsive movements. There were drooling and incontinence of bladder and bowel. These attacks originally occurred about once or twice a month, but in recent years there had been 15 to 20 a month. According to relatives, there had been some "spells" in childhood. The man became increasingly irritable and tired, and a month prior to hospitalization had to go to bed because of fatigue and staggering gait. He became depressed and cried for no apparent reason. Episodes of incoherence became increasingly frequent. In 1939 he had had a thyroidectomy. In November, 1942, he reported to the Illinois Eye and Ear Infirmary with the complaint of poor vision for two years. Bilateral cataract was found, and extractions were done on Dec. 8, 1942, and Jan. 19, 1943. The diagnosis on discharge was senile cataract. There was a vague history of gradual diminution of vision and of tinnitus in the left ear, of unknown duration. In the month prior to hospitalization he became weak and confused, mumbled, and was unsteady in walking.

Examination on admission showed no abnormalities in the general physical examination except for the thyroidectomy scar. He was lethargic and responded slowly and inadequately. The left optic disk was pale, and the right one appeared elevated. There was nystagmus on right lateral gaze, the Romberg sign was strongly positive, and gait was impaired, with falling to the left in both. The stretch reflexes were hypoactive throughout the body; the abdominal and cremasteric reflexes could not be elicited, but there was no Hoffman or Babinski sign. Dysmetria, asynergia, and adiadokokinesis were present bilaterally, being especially pronounced on the right. Lumbar puncture revealed clear, colorless fluid, under a pressure of 140 mm. of water. There were 5 lymphocytes per cubic millimeter and 70 mg. of protein and 68 mg. of glucose per 100 cc. Serological tests for syphilis gave negative reactions. Extensive blood chemistry examinations (without calcium and phosphorus determination) gave values within normal limits. Plain roentgenograms of the skull and chest revealed no abnormalities. There were generalized abdominal distention and urinary retention. On Sept. 5, 1948, the patient was more lethargic and was roused with great difficulty; his condition appeared to be deteriorating. The peculiar seizures, elevated right optic disk, and neurologic findings suggested a brain tumor. Accordingly, on Sept. 8, with the patient under general anesthesia, and with the percutaneous technique, a right carotid angiogram was obtained, revealing no abnormalities. The patient was then placed in the sitting position, and a pneumoencephalographic examination was done, helium being used to replace 180 cc. of spinal fluid. Except for some increase in the subarachnoid spaces, no abnormality was disclosed, and the ventricles were well filled. That night the patient had a grand mal seizure, and the following morning, several Jacksonian seizures occurred, beginning in the left hand. These were controlled with anticonvulsants. There were pill-rolling movements of the left hand. The preoperative lethargy and weakness continued, and clinical signs of bronchopneumonia developed. On Sept. 11, he had laryngospasm and stridor, and that day he died.

Autopsy revealed the cause of death to be bronchopneumonia. No thyroid or parathyroid tissues were found at autopsy. The brain appeared grossly normal and was fixed in formaldehyde solution. Cross sections revealed no abnormalities. However, when routine sections were cut, evidence of hyalinization and calcification of cerebellar capillaries was found. This led to a more detailed study of the brain. Numerous sections of the cerebral cortex were made and stained by Nissl's method and with hematoxylin and eosin. These all appeared normal. Sections of the cerebellar cortex showed normal Purkinje cells, granule cells, and cells of the molecular layer. The report follows: "In the folia of the cerebellar cortex nearest the white matter, however, there are found hyaline bodies with pale and homogeneous centers and a deeply staining rim. Longitudinal sections of the capillaries shows small refractile bodies scattered in the walls and outlining them. Larger vessels, nearby, appear normal. In part of the granular

Fig. 1.—Thionine-stained section of the dentate nucleus of the cerebellum. The small spherules can be seen to be separate in some blood vessel walls and to be fused in others. The nerve cells are heavily pigmented.

Fig. 2.—Thionine-stained section of the ventromedial portion of the globus pallidus. Here the deposits of calcium are larger and denser and in places have formed larger aggregates. The nuclei of the neurones are eccentric, and the Nissl substance is relatively sparse.

layer, the vessels stand out in hematoxylin-eosin sections, with some falling out of nearby cells. Not every vessel is surrounded by the amorphous pale-bluish bodies. Still deeper in the white matter of the cerebellum are larger vessels, with accumulations of bluish staining material. In the dentate nuclei (Fig. 1) the tissues are intensely filled with bluish spherules, and almost all the cells show a brown-yellow lipid material. The same bluish deposits are seen in Nissl-stained sections, in the white matter, and in the cerebellar cortex nearest the white matter. In the pons, the only deposits are seen as very small granules near nuclei of the endothelial cells of capillaries. The larger vessels, deep in the white matter of the pons, appear normal.

"No abnormalities are seen in sections of the temporal lobe and the hippocampus. In the sections of the basal ganglia, vessels in the head of the caudate nucleus have small blue, refractile bodies in the capillaries; round refractile bodies are seen elsewhere, as in the cerebellum. Still other vessels show larger excrescences and coalescence of deposits. These bluish deposits are not seen in the internal capsule or the putamen, but are plentiful in the globus pallidus. No deposits are seen in the thalamus or the substantia nigra. Near the deposits in the white matter of the cerebral hemisphere lateral to the basal ganglia are clusters of nerve cells. Where the deposits are most intense in the globus pallidus and the caudate nuclei, the nearby nerve cells have decreased Nissl substance and eccentric nuclei (Fig. 2). The granules do not stain with Turnbull's blue (ferrous ferricyanide); neither did they give Kossa's reaction for calcium."

Manifestations of Hypoparathyroidism in Four Patients

Manifestation	F. A.	B. K.	E. F.	F. W.
Idiopathic hypoparathyroidism	..	+	..	..
Postoperative hypoparathyroidism	+	..	+	+
Tetany	+	+	+	+
Epilepsy	—	+	+	+
Mental retardation	—	+	—	+
Psychiatric disturbance	—	+	—	+
Papilledema	+	—	—	+
Other neurologic changes	—	—	—	+
Cerebral calcification	—	—	—	+
Roentgenographic calcification	—	—	—	—
Cataracts	—	+	+	+
Electroencephalographic abnormalities	+ (3 tests)	+ (3 tests)	+	Not done
Pneumoencephalographic change	—	Not done	Not done	—

COMMENT

These cases exemplify many of the manifestations of hypoparathyroidism (Table). Although tetany was found in all four cases, it was the presenting symptom in only one. Two patients came because of seizures and cataract; the fourth had generalized weakness, mental dulling, and difficulty in gait. "Senile" cataract in young people or persons of early middle age, with or without a history of thyroidectomy, should lead to investigation of the calcium balance. Any patient with neurological disease, especially with seizures, papilledema, or persisting headache, who has had a thyroidectomy should have tests for hypocalcemia and hyperphosphatemia. It is true that usually the parathyroid glands will not be found to be implicated, but such investigation may spare the patient one or more neurosurgical diagnostic procedures. Neurological examination of patients with epilepsy should include attempts to elicit the Chvostek and Trousseau signs, as well as a test of the effects of hyperventilation. Signs of tetany should be followed by the proper laboratory studies. Technicians who carry out electroencephalographic recordings should be made familiar with the signs of tetany and should observe their patients while hyperventilation is carried on.

For two patients in this study electroencephalographic abnormalities were found with epilepsy; the third had a history of "spells" in infancy. The only patient who was without convulsions had repeatedly normal electroencephalographic recordings. Such findings would tend to confirm the impression that seizures occur with hypocalcemia (and hypoparathyroidism) only when there is some hereditary or other predisposition (in the case of E. F. the congenital deformity of one leg and the other neurological findings indicate prenatal damage). It would appear worth while to study electroencephalographically the families of patients with hypoparathyroidism and epilepsy.

The occurrence of calcification in the basal ganglia and dentate nuclei of the cerebellum is not restricted to hypoparathyroidism and is not necessarily accompanied by neurological symptoms. A quantitative factor must be responsible for the failure to visualize the calcification in the roentgenograms in the case of F. W. The location of the calcification is of interest because of its occurrence in loci of the gray matter which are involved in other diseases, particularly in asphyxia, carbon monoxide poisoning, and nuclear jaundice (*Kernikterus*). The calcium deposits are primarily in the walls of blood vessels, and the damage to the nuclear structures in the aforementioned disorders appears to be related to the oxygen supply. Why these sites should be the most obviously disturbed locations is by no means clear; the characteristics of the circulation in the basal ganglia are not well understood.

In one of the cases of this series (F. A.) doses of parathyroid hormone of 100 units given every two days for a week had no effect on the blood calcium level; unfortunately, no phosphorus excretion study has been carried out on this woman, with post-thyroidectomy hypoparathyroidism. In the discussion of the case of pseudohypoparathyroidism presented by Bishop and DeMowbray,[71] F. T. G. Prunty mentioned failure of 40 units of parathyroid extract to change the chemical balance in a patient with post-thyroidectomy hypoparathyroidism; however, after administration of 200 units in a single dose, the smaller dose was effective. Why such doses should not be effective is unclear. One would not anticipate the occurrence of any phenomenon, such as failure of the end-organ to respond, as in pseudohypoparathyroidism (Albright, Burnett, Smith, and Parson; Albright and Reifenstein; Alexander and Tucker).

SUMMARY AND CONCLUSIONS

There are numerous and varied manifestations of hypoparathyroidism in the central nervous system, as well as in the peripheral nervous system. These include epilepsy, mental retardation, psychiatric disturbances, papilledema, cerebellar dysfunction, cerebral calcification, and electroencephalographic abnormalities. At times, the changes may mimic brain tumor to the extent of necessitating neurosurgical diagnostic procedures or exploration.

These changes in the central nervous system may be the presenting symptom in patients with idiopathic hypoparathyroidism or in patients who, having had thyroidectomy, later manifest hypoparathyroidism. Tests for tetany should be a routine part of a complete neurological examination, and blood studies should be made when any suspicion of the coexistence of disease of the central nervous system and

of the parathyroid glands arises. The index of suspicion should be higher when there is a history or finding of "senile" cataract in a person below middle age or when there has been a thyroidectomy.

The mechanism of the production of the changes in the brain is unknown. The reason for localization of the cerebral and cerebellar calcification in some cases of hypoparathyroidism (seen on x-ray or postmortem examination) is unknown, but this location corresponds to the locus of damage to the gray matter in cases of carbon monoxide poisoning, asphyxia from other causes, and nuclear jaundice in erythroblastotic infants.

Three cases of post-thyroidectomy hypoparathyroidism and one case of idiopathic hypoparathyroidism are reported to illustrate the variety of manifestations of this disorder.

Epilepsy in patients with hypoparathyroidism is probably a reflection of hereditary, traumatic, or other predisposition, as manifested by abnormal electroencephalograms.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Harold C. Voris, M.D., *President*

Leo A. Kaplan M.D., *Secretary*

Regular Meeting March 10, 1953

Use of Piromen in Multiple Sclerosis: A Preliminary Report. Dr. Eugene J. Chesrow and (by invitation) Dr. Edward A. Piszczek, Dr. Harry H. Garner, and Dr. Sherman E. Kaplitz.

This project, involving 19 patients, was started in October, 1951, in the medical wards of the Cook County Institutions, Oak Forest, Ill.

Neurological diagnosis was confirmed in all cases. The ages ranged from 34 to 60. One-third this number was considered semiambulatory; one-third were wheel chair patients; the remaining one-third were bedridden.

Piromen, a bacterial pyrogen, containing 10 γ per cubic centimeter, was used in conjunction with vitamin A and ascorbic acid. To these patients was administered 0.33 + cc. of Piromen (equivalent to 3.33 γ per dose) subcutaneously twice a day, with 50,000 units of vitamin A and 300 mg. of ascorbic acid a day.

Of this group, seven patients are still under active treatment and observation. Two have shown progressive improvement and are continuing to do so at the time of this report. Two patients noted an improvement covering a period of several months with no further changes. One patient complained of getting worse; however, after several months he began to improve. Another patient revealed no change for one year and then noted improvement. One patient was worse at the beginning of treatment and showed no change thereafter.

The remaining nine patients were treated for periods ranging from one month to a year. In this group little or no improvement was noted, and it was at their request that further treatment and observation were discontinued.

Of the remaining three patients, two left the hospital during the course of their treatment, and one died of intercurrent bronchopneumonia a year after treatment was stopped.

Improvement was noted predominantly in the motor system (decreased spasticity) and in bladder control. Piromen, although not a cure, can be used as an aid in the treatment and care of multiple sclerosis.

DISCUSSION

Dr. W. F. Windle: I am pleased to hear of the work done on multiple sclerosis. The Baxter Laboratories are making no claims for the use of Piromen in multiple sclerosis. We are glad to hear of the results of clinical trials. Dr. Kaplitz and his co-workers should be congratulated on their persistence in this difficult study.

Existence of a Suppressor Mechanism, Area 4s, in the Unanesthetized Human Subject. Dr. Russell Meyers, Dr. John Knott, Dr. Miles Skultety, and Dr. Robert Imler, Iowa City.

Suppression, assumed to be a variety of inhibition, has been studied most intensively in Area 4s of the anesthetized cat and subhuman primate. Whether it constitutes a mere artifact of anesthesia remains to be determined. The present inquiry endeavored to deal with three questions: Can electrical and/or motor suppression be induced from Area 4s in the human brain? What effect does general anesthesia exhibit in facilitating suppressor phenomena? What roles, if any, are played by the caudate nucleus, the anterior limb of the internal capsule, and the subcallosal fasciculus in the "subcortical mechanism" of suppression?

Two approaches were employed: (1) electrical and strychnine (3%) stimulation of exposed Area 4 γ, Area 4s, and the caudate nucleus, combined with (*a*) continuous electrographic recordings from representative areas of the exposed cortex and caudate nucleus and (*b*) concomitant observations of the effects of such stimulation on myotonus, motor power, and the "threshold" of Area 4 γ (6 cases); and (2) the effects of extirpation of certain subcortical structures (Question 3 above) on myotonus, motor power, and "release," if any, of hyperkinetic phenomena (18 cases). The results, under the conditions of study, appeared uniformly negative. As conventionally defined, electrical and motor suppression were not observed after stimulation, and no "release" of spasticity, hyperreflexia, or hyperkinesia followed the subcortical extirpations.

DISCUSSION

DR. THEODORE RASMUSSEN: I was most interested to hear about this detailed effort to find evidence of an Area 4s suppressor mechanism in man. Although one must be cautious in saying that a negative result of stimulation indicates the absence of a particular function, these results must call for a restudy of the data in the previous animal experiments that led to the mapping of cortical suppressor strips.

In my personal experience with cortical stimulation in patients, with use of local anesthesia, clear-cut inhibition of voluntary motor activity has been seen in only two. In the first, it was elicited from the second somatic sensorimotor area just above the fissure of Sylvius, and in the second it was elicited from the cingulate gyrus at the level of the anterior margin of the precentral gyrus. I have never noted such a response from any other region of the cerebral cortex, but I was not primarily interested in this phenomenon and the significance of my negative observations is therefore open to question. The results of Dr. Meyers' careful study, however, seem to me to be highly significant and emphasize the need for further studies in clarifying the whole problem of suppression of cortical activity.

DR. PERCIVAL BAILEY: I have seen the phenomenon of suppression time and time again in the macaque and the chimpanzee and have seen it once in the human being. I believe that there is such a phenomenon; its explanation is a different matter.

Logically, of course, the conclusion to be drawn from Dr. Meyers' observations is that he did not stimulate Area 4s. The only evidence we have of the location of Area 4s is through the effect of its stimulation. Does that sound reasonable? If we were concerned with a macaque, I should say no. In the macaque the area is on the surface and easily localizable. In the chimpanzee and man conditions are different and Area 4s may be buried deep in a sulcus. It is quite possible that Dr. Meyers might stimulate the cerebral surface in a half-dozen human beings and still not stimulate Area 4s. We need more observations. Perhaps some day someone will find the area again. These experiments of Dr. Meyers are very interesting, and I admire his persistence in searching for data on the human brain which may be useful in solving some of the difficult problems of motor defects.

DR. GERHARDT VON BONIN: I should like to add a few words on the anatomy merely to tone down the findings of Area 4 γ, Area 4s, etc. Our latest anatomical mapping does not show any of these details; it indicates merely Area 8, in front of the agranular field. It is impossible to differentiate Area 4s by histologic means, but one can differentiate Area 4 and Area 6.

I should like to ask Dr. Meyers what is the mechanism that often cures these patients. What does he think happens as a result of the extirpations which he performed?

DR. RUSSELL MEYERS, Iowa City: The demonstration of what Dr. Rasmussen referred to as "relaxation" obtained from stimulation of the secondary, or supplementary, motor cortex takes us, I believe, into quite another realm of inquiry. To my knowledge, these regions have not generally been represented as suppressor areas, and therefore any attempt to extend my remarks to include them would be extremely risky. In the present paper, I have endeavored to limit myself to the suppressor problem. However, a question occurs to me in connection with Dr. Rasmussen's experience. Given the circumstance that the patient is holding his hand in a flexed posture at the time of stimulation of the secondary, or supplementary, motor cortex and that the hand is then opened, does it follow that this is the consequence of the activation of

a suppressor mechanism? Might it not be that extensor movements have been evoked? Unless we can rely upon the answer to this question, such observations as have been reported by Dr. Rasmussen will have to be regarded as presumptive, rather than conclusive, evidence.

With regard to Dr. Bailey's remarks, I concur wholeheartedly in his opinion that no final conclusions can yet be drawn from our studies. They will have to be extended much further. This we are in the process of doing. It is also our intention to repeat the experimentation on cats and monkeys under conditions simulating those of the earlier experimenters. Already, one critical study of suppression arising from observations on the cat has been published by Dr. Druckman. I have also cited the negative results obtained by Drs. Clark and Ward in the unanesthetized monkey. It must be acknowledged, I think, that these negative data prompt some questioning of the validity of the concept of suppression and suggest the need for further intensive and extensive researches along this line. Our role has been to deal with the problem in the human. I might also remark, as I did not have time in the paper, that our investigation was not limited to the cortex on either side of the precentral sulcus, where Area 4s has been repeatedly depicted. We covered the better part of the dome of the precentral and the postcentral gyrus. Furthermore, in order to get down to the bottom of the sulcus, we incised the arachnoid membrane which bridges across the sulcus and were thus able to put the bipolar electrodes down a distance of about 1 cm. While Dr. Bailey's objection on topographic grounds might be supportable, I wonder whether he would not grant that our results of stimulaitng the caudate nucleus by electrical means and strychninization are not valid. This structure can hardly be mistaken when it is exposed to direct view. Dr. Bailey will recall that our observations failed to demonstrate spikes in the caudate nucleus upon stimulation of Area 4s and that, in the reverse direction, the evocation of spikes by direct stimulation of the caudate nucleus failed to give electrical or motor suppression in the cortex.

In asking what motor mechanism is responsible for the hyperkinesia of the patients upon whom we have operated, Dr. von Bonin asks a most pertinent question. I do not know what the mechanism is, normal or abnormal. To enter into an abstruse discussion of this question would be beyond the scope of the present paper. I can say in general, however, that I am now convinced that until and unless fundamental formulas concerning the so-called pyramidal and extrapyramidal systems are brought under considerable revision, it may be expected that there will be no satisfactory concept of the pathogenesis of the hyperkinetic disorders and of the effects of surgery upon such disorders.

Intramedullary Tumor of the Spinal Cord: Report on Six Cases. Dr. Milton Tinsley and Dr. Archibald D. McCoy (by invitation).

Of six intramedullary tumors of the spinal cord, three were astrocytomas, one a spongioblastoma multiforme, one an ependymoma, and one a dermoid. Two were in children—a girl aged 10 years, with a spongioblastoma multiforme in the midthoracic region, and a boy aged 11 years, with an astrocytoma in the lower lumbosacral portion of the spinal cord. Pain was a presenting symptom in five patients, and this invalidates the textbook differentiation of intramedullary and extramedullary tumors on the basis of early or late appearance of pain. There is no question that all intraspinal tumors should be explored. When the lesion is extramedullary, the attempt at radical extirpation is not questioned. When a lesion is intramedullary, and especially if it is high in the cervical part of the cord, or when the preoperative neurological deficit is mild, the surgeon tends to become very cautious. The six cases reported illustrate the feasibility of radical resection of the tumor at any level and the relatively mild after-effects, even with extensive resection.

Finally, a word to reiterate the feeling of most neurosurgeons that early operation be done in all cases with lesions that can be localized by clinical findings or myelography, even in the absence of spinal fluid block, the operative results being directly related to the duration of involvement of the cord.

DISCUSSION

Dr. Archibald McCoy: In the little girl who had symptoms of a neoplasm of the spinal cord the tumor was obviously intramedullary. Dr. Tinsley removed the tumor himself. He had a great deal more courage than I had.

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Richard M. Brickner, M.D., President New York Neurological Society, Presiding

Joint Meeting, Nov. 10, 1952

Management of Acute Episodes in Multiple Sclerosis. Dr. Richard M. Brickner.

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DISCUSSION

Dr. Israel Strauss: It is difficult to discuss this subject. In the first place, all are agreed that in a disease the cause of which is not known one is sometimes in doubt as to what the treatment does, even though it appears to be effectual. The pathology of multiple sclerosis has not yet given us a certain clue as to the etiology. Putnam's work has in certain respects a bearing on the disease, but some neuropathologists have not agreed that circulatory disorders can be looked upon as the etiologic factor that prevails in all cases of this disorder. Yet it is evident from Dr. Brickner's work that changes in the circulation may be very largely responsible for the development of the changes seen in the central nervous system.

My colleagues and I have tried other methods; some of my patients have received bishydroxycoumarin (Dicumarol), and sometimes it has been successful. I know of other cases in which the disease progressed, sometimes to a fatal end, despite everything we did toward changing the blood coagulability, dilation of the vessels, etc. What Dr. Brickner has demonstrated here is of value. Why does the circulatory disturbance—if that is a factor in some patients and not in others—provide a cause for change in the reactive processes, so that there are permanent, as well as transitory, changes?

Dr. Cornelius H. Traeger: For many years Dr. Brickner has been actively engaged in research on the clinical aspects of multiple sclerosis. He is entirely aware of all pitfalls which may be encountered in evaluating the response of multiple sclerosis patients to any new therapeutic approach.

In this study, he has been able to recognize and effectively to control these errors by the use of placebos and other rational techniques, so that the effects he observed must be considered as genuine physiological responses to the therapies involved.

Basic research dealing with theories of etiology is presently being assiduously pursued in many laboratories throughout the world, and it is to be hoped that, as a result of these many investigations, the mystery of the etiology of multiple sclerosis will soon be solved.

Because of the scientific thoroughness of this study, Dr. Brickner has suggested an extremely feasible treatment program, which can easily be accomplished by the cooperation of the patient and the physician. It is not too much to hope that this program of therapy might well control for long periods some of the more distressing symptoms of multiple sclerosis. The fear of anticoagulation measures, which formerly attended their use, is no longer of serious importance. The availability of simple tests of prothrombin time and the prompt reversibility of the untoward effects with vitamin K_1 have made anticoagulant therapy less fearsome. It is my sincere hope that the basic phenomenon of apparent reversibility of symptoms by vasodilation will be explored in many more of the symptom complexes of multiple sclerosis.

Dr. Alexandra Adler: If it is Dr. Brickner's purpose to increase circulation and to dilate vessels, would it not be preferable to use simpler methods, such as those applied in the management of cerebral anemia, e. g., lowering the head, and bandaging and compressing the abdomen?

Dr. Mary A. Marcus: In view of the fact that hyperinsulinism is at times diagnosed and treated as multiple sclerosis, how can we guard ourselves against making such a serious mistake? In what state of hyperinsulinism would treatment of this kind be indicated?

Dr. Israel Strauss: One of the important factors in treatment is that which Dr. Brickner pointed out, i. e., that when a patient with multiple sclerosis manifests a new symptom he should be attended to at once. With the method Dr. Brickner uses, he probably will be successful in relieving a patient of new symptoms, even though the latter must continue to be a victim of this disease. It will take a great deal of a physician's time to do the work as well as Dr. Brickner does it, for the procedure is time-consuming; but it may be worth while.

DR. DONALD J. SIMONS: Is there evidence through direct observation of the central nervous system that the drugs which produce flushing in the skin actually produce vasodilation in the central nervous system?

DR. RICHARD M. BRICKNER: With regard to Dr. Adler's comment about affecting the circulation by lowering the head, the point is to relieve what are probably constrictions of individual blood vessels rather than to cause a general increase in the circulation. On the other hand, it quite possible that some of the devastating effects of flushing may be due to a blanching of the nervous system, a draining of too much blood from it, so that even if one would relieve moderate constrictions of blood vessels there would be less blood in the brain than before. For this reason, Dr. Adler's suggestion could be very useful. It would, of course, not influence the situation in the spinal cord.

In reply to Dr. Marcus, I should think the differentiation of multiple sclerosis and hyperinsulinism would rest upon the usual criteria for differential diagnosis.

I was glad that Dr. Strauss spoke of the emergency nature of new phenomena in multiple sclerosis. I have come to regard them as emergencies that should be taken care of at once.

As to the time consumed in giving treatment, I do not believe any physician could do it feasibly by himself. I have been very fortunate in having associated with me Miss Gertrude Clark, who has been vigilant and assiduous all the time. Without her I could never have carried out this work.

Dr. Simons raised the question of direct observation of the pial blood vessels after administration of these drugs. Cobb and his associates observed them in animals given carbon dioxide. Matthew Moore observed them with nicotinic acid long before we started this work. From Hare and Constable's studies of the effect of amyl nitrite on spinal fluid pressure, we have collateral evidence of its dilating effect on intracranial vessels.

Parkinsonism and Brain Tumor. DR. MURRAY E. MARGULIES.

W. K., a white man aged 64, who was right-handed ,began to complain of headaches, usually confined to the back of the head, in 1945. Shortly after this, stiffness of the hands was noted. A physician who was consulted made the diagnosis of hypertension. The patient continued to get worse; stiffness of the hands became severer; changes in facial expression were noted, and in 1948 mental symptoms appeared. The patient became forgetful and slow, talked little, and avoided people. A neurologist was first consulted on June 22, 1950. His diagnosis was hypertensive and arteriosclerotic cerebrovascular disease with early Parkinsonism. Roentgenographic examination in September, 1951, revealed a suspicious area in the right lung, and the patient was therefore sent into a hospital with the diagnosis of bronchogenic carcinoma with metastases to the brain. However, bronchoscopic examination failed to reveal a neoplasm in the lung.

Neurological consultation was then requested. At this time the patient showed pronounced bilateral rigidity and spasticity, with masked facies and a bilateral Babinski toe sign. He was apraxic and aphasic and incontinent of urine and feces. It was believed that the clinical course and the clinical picture were not typical of hypertensive encephalopathy and Parkinsonism. Therefore a pneumoencephalogram was done. This revealed that the ventricular system was distorted on the left side and displaced to the right. In view of these findings, pterygoid craniotomy was performed on Jan. 4, 1952, and a meningioma of the sphenoidal ridge was completely removed. The patient showed remarkable improvement within a few months after the operation. The rigidity almost entirely disappeared. He stopped drooling saliva. Memory improved. He regained control of the sphincters and became active and interested in his surroundings.

DISCUSSION

DR. A. M. RABINER: For years this patient had symptoms that were a mixture of Parkinsonism and those due to the brain tumor. The increased intracranial pressure and spasticity of corticospinal tract origin caused lessened motor activity and accentuated the Parkinsonian rigidity. The Parkinsonism, however, seemed the dominant clinical picture, and the presence of an expanding intracranial lesion was not appreciated until his admission to the hospital for a suspected tumor of the lung. After removal of the meningioma, speech returned to normal, there was rapid restoration of motor power in all extremities, and, as was evident at this

presentation, there are now only mild evidences of Parkinsonism. It is of interest also that the hypertension noted prior to operation is no longer evident; and this is a phenomenon that has been often observed in our clinic.

DR. ISRAEL STRAUSS: I should like to ask Dr. Margulies what happened to the roentgenogram of the right lung. He said that there was evidence of a tumor and the bronchoscopic study did not show it; but a tumor does not always have to appear on bronchoscopy. Did you have another roentgenogram?

DR. MURRAY E. MARGULIES: Yes, I did. The patient was studied on the chest service, and it was thought that the shadow was an area of lipid pneumonitis. He had been taking liquid petrolatum for years, and the habitual use of the oil may have explained the lung changes seen with x-rays.

DR. STANLEY LESSE: At the Montefiore Hospital, Dr. Martin Netsky and I reviewed 207 cases of metastatic tumors involving the neuraxis. In 29 of these cases lesions in the basal ganglia were noted at necropsy, but in none was there any clinical evidence of such lesions. Recently, at the Neurological Institute, Dr. Daniel Sciarra and Dr. Bertram Sprofkin reviewed a series of cases of brain tumors in which lesions of the basal ganglia were demonstrated clinically. I believe the discrepancy in the two series is as follows: At the Montefiore Hospital the patients we studied were chronically ill with cancer and had pyramidal tract signs that masked the signs of lesions of the extrapyramidal system, while at the Neurological Institute the patients were more acutely ill and showed a purer picture of basal-ganglion lesions. In private practice, recently, I saw a patient with a metastatic tumor originating in the breast, involving the neuraxis, who presented a hemi-Parkinsonian picture, and who subsequently had a hemiplegia on the same side, with disappearance of the Parkinsonian manifestations within two weeks.

DR. A. M. RABINER: If it were not that this man was suddenly suspected of having a lung tumor, he would still be walking around with the meningioma.

DR. ISRAEL STRAUSS: That would be because you did not pay attention to the constant headaches and vomiting.

DR. MURRAY E. MARGULIES: I have considerable respect for Dr. Rabiner's comment that this patient probably has two diseases. However, I am not entirely certain whether the tumor did not compress the basal ganglia and produce the clinical picture that the patient presented before the operation. We are happy to have seen this excellent result. However, only the microscopic examination of the basal ganglia, as well as the premotor cortex and its connections, can give us a definite answer.

Significance of Development of Grand Mal Seizures After the Age of 35. DR. LOUIS BERLIN.

It is current teaching that seizures appearing for the first time in adulthood are expressions of damage to the brain by tumors or by vascular or degenerative disease. Because my impression did not agree with this, I reviewed the records of 123 patients whose grand mal seizures appeared for the first time at or after the age of 35. These were ambulatory patients who had no gross neurological defects and whose spinal fluid examinations shed no light on the cause of the seizures. The age of onset ranged from 35 to 67. The seizures had been recurring from 6 months to 29 years. Fifty-three of the patients had had seizures four or more years without progressive neurological changes; 47 had pneumoencephalograms; 3 had ventriculograms, and 1 had an arteriogram. Abnormalities were found in only four; in three they were atrophic changes due to old closed head injuries, and in one an atrophy due to cerebral thrombosis occurring 14 years after onset of the seizures.

It appears from our own series, and from the reports of others, that only 5% of patients with tumors have grand mal seizures for more than one year without presenting additional neurological abnormalities. At the time that the only functional disturbance caused by a brain tumor consists of grand mal seizures it is unlikely that contrast air studies will reveal the tumor.

Only nine patients had psychological disturbances indicative of a structural lesion of the brain. Forty patients had had severe closed head injuries, alcoholism, hypertension, or coronary artery disease, alone or in combination, before the onset of seizures. Nevertheless, 60% showed no chronic, systemic, or neurological disease to explain the seizures.

Of the four of these patients who died 2 to 15 years after the onset of seizures, only one showed areas of encephalomalacia that might be related to the development of seizures.

Although careful investigation and vigilant follow-up study are necessary for every patient who has onset of grand mall seizures after the age of 35, it appears that at least 50% of these patients are free of destructive or degenerative brain disease and have a good prognosis.

DISCUSSION

DR. CARMINE T. VICALE: I have little to add to the paper presented by Dr. Berlin. It contains many interesting facts. I regret, however, that it failed to answer some of the problems that confront the clinician when a patient has as the chief complaint grand mal seizures and nothing in the neurological examination, in the roentgenogram of the skull, in the spinal fluid, or in the electroencephalogram to shed any light on its probable cause. Dr. Berlin's paper shows without doubt that a large percentage of grand mall seizures beginning after the age of 35 are not due to brain tumor or to other clinically detectable structural lesions of the brain. It is unfortunate that his series was selected in such a way as to fail to indicate just what percentage of grand mal seizures beginning after the age of 35 is likely to be due to an unknown, rather than to a known structural, cause.

A point made by Dr. Berlin deserves to be stressed, namely, that when seizures are the only manifestation of brain tumor, when everything else is negative, a pneumoencephalogram is very likely to be negative and does not in any way rule out a brain tumor.

Another point is especially noteworthy, i. e., that when grand mall seizures are the only manifestation of brain tumor, in well over 90% of cases, within a year at most, other symptoms will develop which will reveal tumor as the basis of the seizures.

I should like to ask Dr. Berlin whether he has any electroencephalographic data on these patients, and, if so, whether the electroencephalogram was in any way helpful and whether he was able to derive any diagnostic aid from the formal psychometric studies.

DR. E. D. FRIEDMAN: I have little to add except to say that I still would adhere to the thesis that every patient with epilepsy developing in adult life, without a history of seizures dating back to early life, should be carefully examined from time to time until the tumor declares itself. I have had cases in which the tumor first became manifest 10 to 12 years after the first convulsion.

DR. S. P. GOODHART: One sees many patients past the age of 35 who are referred for having experienced one convulsive seizure, this being usually of the typical grand mal type. In my many years of experience as psychiatric consultant to the police department, every once in a while cases of this type have come to my notice. There is no history of alcoholic indulgence, nor does the history divulge attacks in early life. Occasionally these men show, on examination, no clinical suggestion of organic neuropsychiatric pathology. Careful questioning, however, has not infrequently brought out a history of convulsive seizures in early life. I have seen several cases in which typical generalized epileptic attacks occurred during the male involutional period. I also recall several instances in which there were atypical psychomotor equivalents in the first and second decades of life and in which a single grand mal attack occurred between the ages of 30 and 50. These attacks were all generalized convulsive seizures and gave no suggestion of localized cortical pathology. I cannot recall any case in which a characteristic electroencephalographic recording disclosed positive changes. The presence, however, of a convulsive seizure of the Jacksonian type is, in my experience, very suggestive of intracranial pathology, and usually a lesion, I think, of neoplastic origin. Indeed, in a great majority of the cases of Jacksonian attacks occurring after the third or fourth decade of life in which one sees other signs or symptoms, suggesting an intracranial lesion, a careful, detailed search for intracerebral tumor should be made. It was only recently my personal sad experience to have erroneously ascribed symptoms of intracranial tumor to cerebral arteriosclerosis until a sudden Jacksonian seizure led me to the immediate recognition of a large meningioma, which was finally successfully removed.

DR. LOUIS BERLIN: To Dr. Friedman I wish to say that every patient, even when he has grand mal seizures at 3 years of age, deserves careful investigation.

As to the use of the electroencephalogram, we had some patients who had normal pneumoencephalograms and normal spinal fluid and whose electroencephalogram was, in retrospect, focally abnormal.

As to whether or not these seizures are idiopathic, whatever that may be, is, I think, a secondary consideration. The practical questions are what should be done to improve diagnostic procedures, what diagnostic procedure is warranted and what is not warranted, and what is the prognosis, regardless of the cause.

DR. PETER G. DENKER: If I understood Dr. Berlin correctly, these 123 patients with grand mal seizures had a normal neurological status, normal roentgenograms of the skull, and normal spinal fluids. It is important to know how many patients with grand mal seizures were excluded from this series to get the total of 123 he studied. This would give a better idea as to the proportion of patients who have grand mal seizures with normal neurological findings.

DR. LOUIS BERLIN: We excluded a great many, but I cannot say how many.

DR. PETER G. DENKER: Was it 2:1, or what was it approximately?

DR. LOUIS BERLIN: I would say 50% at least.

DR. A. M. RABINER: Of all these patients, did only one or two have arteriograms?

DR. LOUIS BERLIN: One of our patients with brain tumor had a normal arteriogram, and one of our patients without a brain tumor who died in status epilepticus had a normal arteriogram.

DR. A. M. RABINER: We should strike a cautious note in regard to this communication. A patient who has a convulsion for the first time after the age of 35 should be considered a tumor suspect. Though the pneumoencephalogram may often show nothing abnormal, one should not establish a rule that a pneumoencephalographic study need not be done.

DR. LOUIS BERLIN: I should like to know of one case on record in which a patient had grand mal seizures alone, with normal clinical neurological findings, normal mental status, and normal spinal fluid and in which a ventriculogram or an encephalogram revealed a tumor. A brain tumor can exist in such circumstances, but the pneumoencephalogram has not been reported to show any abnormality at that stage.

Experimental Epilepsy in the Monkey Following Multiple Intracerebral Injections of Alumina Cream. DR. JOSEPH G. CHUSID, DR. NICHOLAS KOPELOFF, and DR. LENORE M. KOPELOFF.

Clinical, pathological, and electroencephalographic features of chronic epilepsy produced by multiple intracerebral injections of an aqueous suspension of aluminum hydroxide (alumina cream) into sensorimotor cortex of seven monkeys (Macacus mulattus) were reviewed. The intracerebral injections were made in eight standard positions to a depth of 3 to 11 mm. from the cortical surface, with an estimated amount of 0.4 to 0.6 ml. of aluminum hydroxide suspension. In five of the six animals given unilateral injections, spontaneous focal motor manifestations became evident three to four weeks after operation. Initially, the motor epilepsy resembled that described in man as epilepsia partialis continua (Koshevnikoff); spontaneous contralateral Jacksonian motor seizures with spread were most prominent during the next few weeks. Epileptic activity gradually diminished thereafter; accentuation of convulsive activity by excitement, movement, or agitation was the rule. Contralateral hemiparesis of mild to moderate grade was present in all animals. An animal which had been treated by multiple injections into both cerebral hemispheres died in status epilepticus three weeks after onset of seizures.

Postmortem examination disclosed a meningocerebral cicatrix extending over the area of injections, with scarring and rare small-cyst formation in the underlying cortex and subcortex. The needle tracks contained masses of basophilic material and collections of gitter cells; adjacent tissue showed cortical neuronal changes, moderate diffuse gliosis, increased vascularity, and demyelination of subcortical white matter. The deepest injections (11 mm.) were made into the cerebral hemisphere of the only monkey that did not exhibit convulsions and extended into the superior portion of the putamen and the internal capsule.

Serial electroencephalograms made after the injections were characterized by high-amplitude spike and sharp- and slow-wave activity, most pronounced over the treated cerebral hemisphere. These abnormalities were most intense early and roughly paralleled the degree of motor con-

vulsive activity of the individual monkey. Intravenous injections of 0.1 cc of 10% pentylenetetrazole (Metrazol) usually accentuated or precipitated local spike and sharp-wave activity and were sometimes associated with transient contralateral clonic or epileptiform movements.

A motion picture was presented of one of the treated animals manifesting epilepsia partialis continua and spontaneous Jacksonian motor seizures with spread.

DISCUSSION

DR. DONALD J. SIMONS: Will excision of the area in which the cream was injected stop the seizures?

DR. JEFFERSON BROWDER: How long was it after the injection that these spikes appeared? Was that prior to the clinical manifestation of Jacksonian fits?

DR. A. M. RABINER: I got the impression from the moving pictures that there was pronounced paresis in the left upper and lower limbs; so, obviously, a lesion was produced in the right cortex. In what way does injection of this suspension differ from any other type of trauma to the cortex in producing cortical pathology which later results in seizures?

DR. MARY A. MARCUS: Was any attempt made at therapy of these seizures?

DR. JOSEPH G. CHUSID: Excision of the injected area has not been done in monkeys after multiple intracerebral injections of aqueous aluminum hydroxide suspension. However, in animals made epileptic by the application of disks containing aluminum hydroxide suspension over the motor cortex, ablation of the underlying cortical tissue caused a temporary diminution of electroencephalographic abnormalities and suppression of clinical seizures.

High-amplitude spike discharges usually were detected in the electroencephalogram before the onset of clinical seizures. Other substances injected intracerebrally in this fashion may produce similar electrical patterns and associated hemiparesis without clinically obvious epileptiform manifestations.

An attempt at drug therapy was made in the case of the monkey with bilateral intracerebral injections of aqueous aluminum hydroxide suspension which died despite parenteral administration of large doses of anticonvulsants. Treatment was not given to other animals because it was deemed necessary to establish the usual pattern of convulsive response produced by this technique of multiple intracerebral injections of aqueous aluminum hydroxide suspension.

Louis Hausman, M.D., *Chairman, Section of Neurology and Psychiatry, Presiding*
Joint Meeting, Dec. 9, 1952

Clinical Hypothalamic Syndromes. DR. I. S. WECHSLER.

The author described a clinical hypothalamic syndrome which may occur in the course of vascular disease, infection, or compression of the brain or in encephalopathy. It is characterized by a special type of alert coma, generally spoken of as coma vigil. With it there may be restlessness, evidence of sexual excitement, or general psychotic behavior. Focal signs of cerebral involvement usually are absent. With the coma there may be pronounced hyperthermia without the usual signs of fever; occasionally there is hypothermia. There is variation in pulse rate without parallelism between pulse rate and temperature. Frequently there is a drop in blood pressure in patients with known hypertension or fluctuation in blood pressure in previously normal persons. There may be polyuria, transient hyperglycemia with glycosuria, excessive perspiration in the absence of fever, and minor or major convulsions. The coma may last days, weeks, or months. The condition is grave, generally fatal; but there may be recovery without residual signs or symptoms.

The author also alluded to other diencephalic syndromes, among them diabetes insipidus, behavior disorders, variation in states of consciousness, fever of unknown origin, and special petit mal seizures. The last is characterized by extreme pallor, a drop in blood pressure, and an increase in pulse rate. It may yield to Dexedrine (dextrorotary isomer of amphetamine) or ephedrine when it does not yield to sedative anticonvulsants.

The paper included a brief summary of the anatomy of the hypothalamus. More detailed consideration was given to the neurophysiology of the hypothalamus, with special reference to sleep and other states of consciousness. The object of the paper was to correlate known functions of the interbrain with clinical manifestations of their impairment.

DISCUSSION

DR. H. HOUSTON MERRITT: Dr. Wechsler has shown courage in attempting to clarify the problems of the hypothalamus. He has reviewed the anatomy of the hypothalamus, and he has stated that most of our knowledge in regard to the function of the various nuclear masses in the hypothalamus is based on the results of work on animals. He has stressed the fact that great caution should be exercised in using the results obtained in these animal experiments in the interpretation of clinical phenomena in man. Unfortunately, however, most of the information in regard to the physiology of these nuclear masses must come from animal studies.

I shall limit my remarks to a consideration of the clinical syndrome which he considers to be characteristic of hypothalamic dysfunction. The individual features of this syndrome include coma or coma vigil without signs of disturbances in the motor or sensory sphere, elevation of body temperature without increase in pulse rate or leucocytosis, restlessness, hyperglycemia, glycosuria, convulsions, and signs of dysfunction of the autonomic nervous system. He cited a few conditions in which this syndrome may occur, particularly encephalitis and vascular lesions. He did not mention two conditions in which the clinical picture is remarkably similar to that he outlined. These are Wernicke's encephalopathy, which occurs most frequently in alcoholics who are on a deficient diet, and thrombosis of the basilar artery. In both these syndromes the hypothalamus may be damaged. The common sites for the hemorrhagic lesions in Wernicke's encephalopathy are in the mamillary bodies and the neighboring paraventricular nuclei. The basilar artery gives rise to the posterior cerebral arteries, and branches of the latter nourish the hypothalamus. We must remember, however, that in both these conditions, as well as in encephalitis and the other conditions described by Dr. Wechsler, many other areas of the brain are damaged. In Wernicke's encephalopathy there are diffuse changes in the cortical cells, as well as in other parts of the brain, and thrombosis of the basilar artery is accompanied by damage to the reticular substance of the brain stem. We should therefore use great caution in attributing the set of symptoms described by Dr. Wechsler to specific damage to the hypothalamus or to any one portion of the nervous system. It may be that these are symptoms of general cerebral dysfunction and not symptoms of dysfunction of a specific area.

Dr. Wechsler emphasized that this was a clinicophysiological study and that he was not presenting any pathologic material. I would recall Dr. Wechsler's warning that we should not attribute too many functions to the hypothalamus until we know more about its physiology. The hypothalamus is a small amount of nuclear material, but our ignorance of its function is so great as to allow us room to wander around in fanciful speculation.

DR. LOUIS J. SOFFER: I find myself intrigued with this discussion of the hypothalamus. I have been interested in endocrine physiology for many years, and one of the very exciting and speculative areas is the hypothalamus. It is to me of considerable interest that over a hundred years has elapsed since attention was first directed to this area and during this time we have accumulated a certain, or perhaps uncertain, body of knowledge, owed mostly to the efforts of astute physicians and some actual experimental work.

Of great interest at present is the fact that the hypothalamus is concerned with response to anger. With the newer concept of stress, this becomes very important.

The hypothalamus is a difficult area to approach experimentally, and until new modalities of investigation are devised our increasing body of knowledge concerning it will continue to be dependent upon the observations of acute clinicians and ingenious investigators. For this reason I feel that Dr. Wechsler's contribution is an important one, for it represents painstaking clinical observation that brings us another step forward in our knowledge of the hypothalamus.

DR. I. S. WECHSLER: Dr. Merritt and Dr. Soffer's criticisms are well taken. Of course, I realize that there are gaps in our knowledge, but I believe that the syndrome I described has clinical validity. All of us have seen cases of the special coma and the other manifestations I mentioned in which we could not localize the lesions. It is my conviction that this is a hypothalamic syndrome worth bearing in mind.

Pharmacologic Studies in Electric Shock Therapy, with Special Reference to Curare and Anticurare Agents. DR. LAWRENCE H. GAHAGAN.

Cardiodynamic and respiratory exchange studies were made during electric shock therapy on 10 psychotic men who were regularly receiving this treatment. Observations were made under four conditions: (1) without the use of any drug; (2) with intravenous administration of atropine; (3) with intravenous use of tubocurarine chloride, and (4) with intravenous administration of gallamine (Flaxedil).

It was concluded that gallamine is the preferred agent in electric shock therapy because of its strong vagolytic action, which protects against cardiac disturbances. Gallamine in a dose of 1.5 mg. per kilogram provides satisfactory muscular relaxation and adequate blockade of the cardiac portion of the vagus. Use of the anticurare agent edrophonium (Tensilon) chloride was also demonstrated.

DISCUSSION

DR. JAMES H. WALL, White Plains, N. Y.: I should be interested to hear from Dr. Gahagan whether gallamine is effective in inhibiting the violence of the convulsion, as well as in its vagolytic action, and just what is the superiority of this drug over tubocurarine chloride.

DR. LOTHAR B. KALINOWSKY: I have not had any experience with gallamine, but I am still skeptical regarding tubocurarine chloride. That a group of patients has been treated without any untoward effect does not prove much; the fact remains that the splendid experimental studies by Bennett were soon followed by reports on fatalities. In the first large report on electroshock fatalities, all cases of immediate death were of patients who had been given curare. Later, there was the famous case of Riggs and Schlomer, whose patient died before electric shock was given. The only fatality I myself have had in many thousands of electric shock cases was one of the few in which I used curare. Therefore I still feel that until we have much more experience we should not consider any drug as harmless.

DR. WILLIAM HOLT, Albany, N. Y.: I am glad to hear this report on gallamine. I have tested it at the Boston Psychiatric Hospital and am still using it in Albany. I think the succinylcholine chloride will soon replace the gallamine because of its great advantage in the saving of time, which is precious in a busy clinic.

No comment was made on the use of thiopental (Pentothal) with the curare. Will Dr. Gahagan please mention that? Atropinization is an important matter, and atropine should be given when gallamine is used with neostigmine, for the antidote increases the salivation, aspiration of which is one of the hazards in the treatment of the unconscious patient.

DR. LAWRENCE H. GAHAGAN: I shall have to answer these questions largely on the basis of the literature, since my experience with curare and anticurare has been limited to the present study.

As to Dr. Wall's question concerning the superiority of gallamine over the natural curare, natural curare, of course, is used successfully in many places, such as the Westchester Division of the New York Hospital. The basis for the statement as to the superiority of gallamine over tubocurarine in electroshock therapy, the one pointed out in this paper, is that gallamine has a vagolytic action and that this is desirable in electroshock therapy because it prevents disturbances in cardiac rhythm in the immediate postconvulsive period. The vagolytic action of natural curare, on the other hand, is slight.

Another advantage of gallamine is that the dose response is predictable, whereas with curare the response is often unpredictable. It has also been found that gallamine does not block autonomic ganglia. There is no significant fall in the blood pressure, and it has no histamine effect.

With reference to Dr. Holt's statements, I agree that thiopental or amobarbital or some other intravenously administered barbiturate should be given whenever a curarizing agent is used. The objections which he cited are certainly true. Gallamine, atropine, and a barbiturate, such as thiopental, can all be mixed successfully in the same syringe and given intravenously before induction of electric shock. That has been done at the London Hospital, in England, in over 600 treatments (Thompson, O. S., and Norton, A.: Use of Gallamine Triethiodide [Flaxedil] in Modifying E. C. T.: A Comparison with d-Tubocurarine Chloride and Decamethonium Iodide, *Brit. M. J.* **1**:857 [April 21] 1951).

Since gallamine and the natural curare are antagonized by edrophonium, there is no advantage of one over the other in this respect.

Psychological Factors Associated with Disseminated Lupus Erythematosus. Dr. Selwyn Brody.

Lupus erythematosus is a disease which has become prominent since the advent of cortisone. It has been included with the other "collagen diseases," such as rheumatoid arthritis, rheumatic fever, periarteritis nodosa, scleroderma, dermatomyositis, and ulcerative colitis. Although in many respects these "rheumatic states" are similar, especially pathologically, their precise clinical and etiologic relationships are obscure.

The disease was originally described in latter part of the 19th century. At the turn of the century, Osler recognized visceral forms of the disease. In recent years, Klemperer's contributions have been outstanding in clarifying the pathophysiological disturbances of the connective-collagen tissues in these diseases.

Systemic lupus erythematosus is a widespread destructive disease which affects the viscera and brain. The cause is unknown. Selye includes lupus among the diseases of adaptation, emphasizing the role of adrenal cortex physiology. Rich considers allergic hypersensitivity of fundamental importance in the pathogenesis.

The chief signs and symptoms are the "butterfly rash" of the face, arthralgias, arthritis, fever, cough, and pain in the chest and abdomen. Convulsions are not uncommon.

The course is exceedingly variable and uncertain. Repeated remissions and relapses may occur.

When cortisone and corticotropin were introduced in 1949, I became interested in studying the effects of these hormones on the various collagen diseases because of an apparent remarkable connection between the physical symptoms these patients manifested and psychological disturbances.

Observations were made on the psychological development, symptoms, and clinical course of 42 patients who were suffering from this disease process. Eighty-five per cent of them received cortisone or corticotropin or both. The study confirmed the observations that this disease is primarily one occurring in young girls (85%), that it is frequently fatal (26%), and that psychological stress situations appear to have been a consistent factor in the precipitation of the outbreak, recurrence, or exacerbation of the disease. Favorable psychological influences appear to mitigate the severity of the course of the disease. Emotional factors contributed to the therapeutic effectiveness or failure of the hormones.

In the course of this investigation, there were found a dramatic readiness for psychotic episodes (52%) and a remarkable shift from psychotic to nonpsychotic states, particularly during hormone treatment.

Preliminary observations suggest that the development of a sustained psychosis appeared to have a therapeutic effect and served to prevent a fatal outcome. Six patients had a protracted psychosis, and not one has succumbed to the disease, nor did any of the 11 patients who died sustain a prolonged psychosis.

It was suggested that an important factor in determining the outcome, and even possibly the etiology, of the disease is to be found in the type of pattern of behavior with which the ego is built during the first two years of life.

The investigation of this possibility requires careful study of these patients while they are receiving intensive analytic psychotherapy.

DISCUSSION

Dr. Hyman Spotnitz: I have had the privilege of many discussions with Dr. Brody while he has been conducting these important investigations on the psychological aspects of these not very well-known diseases. Dr. Brody has shown a great deal of courage in calling attention to the possibility that the psychosis in lupus erythematosus may have a life-preserving function. There are several possibilities which must be taken into consideration in a discussion of this question of psychosis and lupus erythematosus. First, this psychosis may be an organic one. I should like to ask Dr. Brody whether some of the psychotic manifestations that he observed could be attributed primarily to the organic disease of the brain. Second, the psychosis may be functional. Third, the psychosis may be an organic psychosis that changes the physiology of

the body in such a way as to make it possible for the patient to survive the illness. We may see in the future the development and utilization of drugs and techniques to precipitate psychoses and then to reverse them.

Dr. Brody's studies have impressed me with the great need for the analytic-psychotherapeutic investigation of the patient with lupus erythematosus. It is obvious that if psychological factors are significant in influencing the fatal outcome to this disease, such investigations must be made by carefully trained persons who are aware of their own instinctual needs and the therapeutic, and possibly destructive, significance of their own patterns of ego organization.

DR. LEWIS D. STEVENSON: Have any studies been made to find out whether disseminated lupus erythematosus occurs in animals, other than man, who are subject to severe stress?

DR. FRANZ J. KALLMANN: If murderous impulses formed in the first or second year of life play an essential part in the etiology of lupus erythematosus, may I ask Dr. Brody how he explains the marked sex difference observed by him and other investigators?

DR. SELWYN BRODY: In answer to Dr. Spotnitz' question regarding organic cerebral pathology, I do not think there is any doubt that organic changes play a part in the psychoses, although my personal impression has been that they are often exaggerated, to the exclusion of other factors, such as purely psychogenic ones.

In answer to Dr. Stevenson's question, I have no information on the incidence of this disease in animals.

As to the difference in incidence in males and females, I would suggest that a predisposing emotional factor in this disease may be that females are more sensitive (to their hostile impulses) toward their mothers than are male children. The patients I observed had extreme attachments to their mothers, many of them being the only child.

Psychiatric Aspects of Neurodermatitis. DR. T. L. DOYLE, White Plains, N. Y.

Frequently, dermatologists and physicians are called upon to treat skin diseases which have in their pathogenesis a sick psyche. A review of the literature revealed that diagnostic criteria are essential, as stressed by Walsh and Kierland. Other authors have pointed out that certain personality types are predisposed to a neurodermatitic reaction—those of an obsessional character and those evidencing a deep-seated emotional conflict, with a propensity to vascular disturbance.

Two patients at the Westchester Division of the New York Hospital were treated by a total approach, therapy being directed both toward the skin lesion and the psychic illness, which was considered to operate essentially on the basis of a conversion hysteria. In diagnosis, a complete history must be taken and a complete physical examination made, as well as laboratory tests and biopsies. In the approach to the neurotic problem, one must demonstrate the conflict and show that it arises from opposing internal forces, as well as demonstrate the defenses used. In psychotherapeutic interviews, then, insight can be developed and a reversal of the pathologic mechanism can be established.

PHILADELPHIA PSYCHIATRIC SOCIETY

Frederick Kramer, M.D.

President, in the Chair, Regular Meeting, April 10, 1953

Widening Psychiatric Horizons in the Field of Retardation. DR. EDWARD J. HUMPHREYS, Norristown, Pa.

Mental retardation is a central area in the field of limitations in human development. The psychiatrist is constantly concerned with the problems of human development and therefore should include the subject of retardation as a major interest.

Retardations in human development include physical, intellectual, emotional, and social configurations of the psyche. Some retardations in psychic development may be reflections of imbalance or maldevelopment in elemental psychological or physical structures. A reevaluation of the work of the leaders in constitutional medicine and in the depth psychologies is required by way of further understanding of mental retardations, whether found in the state school, the state hospital, or the mental hygiene clinic. A deepening knowledge of unitive functionings of the psyche is urgently needed.

A modern governmental and community program on mental health is a prime requisite in the redevelopment or mobilization of resources to meet properly the needs of the mentally retarded of whatever category, in terms of treatment, training, control, and prevention. The efficiency of such a program may be locally determined through regionalization of the mental health program. A national and international program of this type is indicated. Heavier investments in research on mental retardation and extensive professional training in the field should be provided.

Role of Emotional Disturbance in Mental Retardation. Dr. Robert C. Prall, Philadelphia.

The role of emotions in mental retardation is receiving increased attention. This paper constituted a preliminary report of the author's experiences as staff psychiatrist at the Training School at Vineland, N. J., working in an interdisciplinary approach with the educators, psychologists and administrators.

This approach offers new insights into the part played by emotional disturbances in the etiology and sequelae of mental retardation.

Etiologically, it has become apparent that many psychiatric diagnostic categories, including the psychoses, neuroses, and personality and behavior disorders, are found in mentally retarded patients in whom the symptoms of the illness have assumed the guise of intellectual retardation and learn disabilities. In many cases the intellectual endowment is apparently higher than the patient's performance has indicated.

In persons who are basically retarded or who have organic cerebral disturbances, concomitant emotional disorders of many types have been found.

The author reports the work being done at the Training School with the education and cottage departments, designed to foster a better "mental health" atmosphere within the school.

Research is being undertaken to determine the accessibility and responsiveness to psychotherapy of both the etiological and the resultant types of emotional disorders. The implications of this work are stressed in regard to professional and community education for the prevention and alleviaton of emotional difficulties, and the necessity of further research.

Psychodynamics of the Mentally Retarded. Dr. Edgar A. Doll, Devon, Pa.

The mentally retarded include (1) persons who are socially incompetent, and (2) those who are marginally adequate. The former include the clinically feebleminded; the latter, the borderline normals. The psychodynamics of these two types differ.

Feeblemindedness is defined as a condition of constitutional hypoplasia. The psychodynamic factors in this group are similar to those of normal children except that the feebleminded are arrested at successive growth levels—infancy, childhood, and preadolescence. The emotional lives of these patients are relatively simple. Emotional suppression or regression is seldom encountered. Disturbances are apparent in feebleminded patients with a psychosis or in those who have had extraordinary emotional trauma.

Among the borderline patients the psychodynamic issues are comparable to those of normal children. Frustration is experienced because there is mentally retarded behavior. These children experience the usual psychodynamic disturbances which beset all children who are subject to unfavorable experiences during their growing period. This group includes children whose developmental processes have been retarded by brain injury, with resultant dynamic disturbances.

Distinctions are drawn between these various groups and types of the mentally retarded for the purposes of understanding, management, and treatment.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

DISTURBANCE OF THE PUPILLARY REACTIONS. J. H. DOGGART, Lancet **1**:1081 (May 19) 1951.

Doggart reviews some of the more recent anatomic and physiologic findings with respect to the pupillary reaction and discusses several clinical entities. He reviews the work of Lowenstein in which it is pointed out that the rapid primary phase of pupillary contraction to light is entirely a parasympathetic phenomenon, whereas the secondary and tertiary phases depend on sympathetic activity. If stimulation by light is followed by an abnormally long latent period, and then by a contraction exclusively effected by the primary phase, the sympathetic system is disturbed. Lowenstein calls this type of response the tonohaptic reaction and has noted its association with catatonia, postencephalitic Parkinsonism, Fröhlich's syndrome, and other disorders. A crude method of differentiating sympathetic and parasympathetic abnormalities exists in pharmacodynamic tests.

The author states that all interpretations of the pupillary signs should be made in the light of up-to-date anatomic observations. The Edinger-Westphal nucleus, from which emerge the pupilloconstrictor fibers, receives excitatory stimuli from the occipital and frontal regions of the cortex, but recent researches have shown that the frontal cortex also sends out inhibitory impulses. In other words, mydriasis, formerly regarded as mediated by stimuli traveling from the frontal cortex to the sympathetic center in the hypothalamus, is really attributable to cortical inhibition exerted on the Edinger-Westphal nucleus.

Another important anatomic feature is the existence of an inhibitory sympathetic pathway from the hypothalamus to the constrictor center, and it is abundantly proved that mydriasis accompanying powerful emotions is achieved not so much by stimulation of the sympathetic fibers as by inhibition of parasympathetic constricting nerves.

One more anatomic fact is emphasized. The old teaching that the afferent pathway of the light reflex relayed in the superior colliculi had to be abandoned several years ago. It is now generally agreed that in man the pupillary fibers leave the optic tracts before the lateral geniculate body is reached. They pass by way of the brachium of the superior colliculus to reach the pretectal nucleus at the junction of the diencephalon and the tectum of the midbrain. Most of the fibers cross the posterior commissure, but some remain on the same side, with the result that fibers from each optic tract enter both Edinger-Westphal nuclei. Thus, stimulation of the pretectal area induces bilateral pupillary constriction.

On the clinical side, Doggart points out that unilateral dilatation and immobility of one pupil rapidly supervening in a case in which at first no pupillary abnormality had been displayed should suggest ipsilateral intracranial hemorrhage, and similar signs are likely to become manifest in the opposite pupil unless the flow is staunched. The mechanism of this phenomenon is not known for certain, but pressure upon the parasympathetic center in the midbrain is often blamed. Traction on the nerve trunk by the tectorial pressure cone is also postulated.

The genuine Argyll Robertson pupil is small, does not react to light but reacts in convergence, and does not dilate under the influence of atropine, though painful stimuli can still produce mydriasis; the outline is seldom a regular circle, and is sometimes quadrilateral or elliptical. The lesion responsible is probably in the upper half of the midbrain near the aqueduct of Sylvius.

Finally, the author mentions several rare abnormalities of the pupil, such as rhythmic contraction and dilatation occurring synchronously with the excursions of nystagmus; voluntary mydriasis and hippus, and cogwheel pupil, in which the diameter waxes and wanes in a series of jerks, instead of describing a continuous sweep.

MADOW, Philadelphia.

Physiology and Biochemistry

MOTION OF THE LUMBAR SPINE. S. S. TANZ, Am. J. Roentgenol. **69**:399 (March) 1953.

Tanz reports on a study of spinal motion in 10 children and 45 adults. The ages of the children were between 2 and 13 years, and the ages of the adults were 35 and over. To-and-fro bending (flexion and extension) and lateral bending of the lumbar portion of the spine were measured and recorded. Some studies of rotation of the lumbar spine were also made, but the results are not included in the report, since Tanz was not able to devise a method of accurate measurement for the degree of rotation. His opinion is that in some persons a significant amount of rotation can occur without lateral bending.

The patients were all clinically normal at the time of the study, although some of the patients gave a history of pain in the low back. No significant difference was found between the findings for these patients and the findings for the patients with no history of pain in the low back.

Both to-and-fro and lateral motions of the lumbar spine are greatest at the younger ages. There is a decrease in the range of both motions in adolescence and young adulthood. After the age of 35 there is no further significant loss of motion. Diminution of motion at one level is usually accompanied by diminution of motion at all levels; there is usually no compensation in the form of increased motion at other levels. The amount of to-and-fro motion did not differ significantly at the various lumbar interspaces. Nor did the amount of lateral motion differ at the various interspaces, except at the lumbosacral interspace, where there was very little lateral motion. There were large individual variations in the range of motion of the lumbar spine from one patient to the next. These variations were so large that Tanz thinks no normal pattern can be established. In general, he does not agree with Begg and Falconer, who established a "normal" pattern of range of motion for the to-and-fro motion of the lumbar spine. Tanz also disagrees with these authors concerning lateral bending, for he found that the average range of lateral bending is about two-thirds as great as that for the to-and-fro bending, whereas Begg and Falconer were of the opinion that the amount of lateral bending was insignificant.

WEILAND, Grove City, Pa.

TRANSAMINATION OF γ-AMINOBUTYRIC ACID AND β-ALANINE IN BRAIN AND LIVER. E. ROBERTS and H. M. BREGOFF, J. Biol. Chem. **201**:393, 1953.

Both brain and brain residues and acetone powders contain enzyme systems which catalyze the transamination of γ-aminobutyric acid and β-alanine with α-ketoglutarate. The rates of these reactions were of the same order of magnitude as those found with alanine and aspartic acid. The transamination of γ-aminobutyric acid and β-alanine with α-ketoglutarate could not be demonstrated in preparations from pepper and avocado, which catalyzed the transamination of alanine with α-ketoglutarate.

β-Alanine could play an important part in nitrogen metabolism because of its transamination with α-ketoglutarate. γ-Aminobutyric acid metabolism involves transamination with α-ketoglutaric acid to form glutamic acid and succinic semialdehyde. The authors confirm the results of Bessman, Rossen, and Layne.

PAGE, Cleveland.

CEREBRAL CIRCULATION AND METABOLISM IN SICKLE CELL AND OTHER CHRONIC ANEMIAS, WITH OBSERVATIONS ON THE EFFECTS OF OXYGEN INHALATION. A. HEYMAN, J. L. PATTERSON, and T. W. DUKE, J. Clin. Invest. **31**:824 (Sept.) 1952.

Sickle cell anemia may be associated with a variety of serious cerebral manifestations. These symptoms are usually attributed to thromboses of the cerebral vessels produced by sickled erythrocytes, vascular stasis, and degenerative changes in the smaller arteries of the central nervous system. In chronic anemias from various causes mental manifestations are often seen. A diminution in cerebral oxygen consumption in patients with pernicious anemia has been reported and may be the basis for the alterations in the mental status seen in these patients.

For these reasons, the authors studied the cerebral circulation and metabolism in a group of patients. The cerebral blood flow, cerebral oxygen consumption, and cerebral vascular resistance were determined by the nitrous oxide technique, before and during the administration of 85 to 100% oxygen, in 10 patients with sickle cell anemia and in 8 patients with chronic anemia of other types, none of whom showed mental symptoms or neurologic involvement.

The mean cerebral blood flow for the patients with anemia as a group was significantly elevated, while the mean cerebral oxygen consumption was moderately reduced below that for control subjects. There were only small differences between the mean values for cerebral blood flow and cerebral oxygen consumption in the two groups of anemic patients.

The administration of 85 to 100% oxygen to the patients with anemia was generally followed by a decrease in the cerebral blood flow and an increase in cerebral vascular resistance comparable to the values found for the control subjects. The cerebral oxygen consumption in many of the patients with anemia showed a rise during oxygen inhalation.

Heyman and his colleagues believe that the increase in cerebral blood flow in chronic anemia is caused by the combined effect of reduction in blood viscosity and vasodilatation from reduction in arterial, mean capillary, and venous oxygen tensions. They further suggest that the reduction in cerebral metabolism, and possibly to some extent the mental symptoms, observed in chronic anemia may be due to chronic tissue hypoxia. The use of oxygen may therefore be a rational emergency therapeutic measure in such cases when mental symptoms are present.

ALPERS, Philadelphia.

FOOD INTAKE AND SPONTANEOUS ACTIVITY OF RATS WITH LESIONS IN THE AMYGDALOID NUCLEI. B. K. ANAND and J. R. BROBECK, J. Neurophysiol. **15**:421 (Sept.) 1952.

In dogs an increase in food intake, a decrease in activity, and a change in character have been observed after bilateral destruction of the amygdaloid cortex. Pribram and associates, similarly, observed "increased food intake" in a baboon with ablation of the entire oribitoinsulotemporal region.

In this study, bilateral electrolyte lesions of the amygdaloid nuclei in rats were shown to be followed by (1) no change in food intake; (2) a marked decrease in spontaneous activity; (3) a fall in body temperature for about a week, and (4) no development of savageness, the lesions having the effect of making a savage rat tamer.

Cats with similarly localized lesions did not exhibt any rage reactions, although they were kept alive for from six weeks to two months. The food intake remained normal in animals in which the lesions did not spread into the lateral portion of the hypothalamus.

ALPERS, Philadelphia.

ON THE ANATOMY OF ANTEROLATERAL CORDOTOMY. E. A. KAHN and R. W. RAND, J. Neurosurg. **9**:611 (Nov.) 1952.

The increasing frequency with which prefrontal lobotomy is being used in cases in which a properly performed anterolateral chordotomy would suffice for the relief of intractable pain is to the authors an indication that the exact technique of the latter procedure is still not common knowledge. In 4 of a series of 63 cases in which anterolateral chordotomy was performed recurrence of pain necessitated reoperation. From a presentation of these four cases and a discussion of the anatomy of the anterolateral chordotomy, the authors summarize the technique of this precision operation as follows:

In performing anterolateral chordotomy at the upper thoracic levels of the spinal cord the point of the knife should enter the cord exactly at the attachment of the dentate ligament. The incision should be carried to a depth of 4 or 5 mm. in a plane making an angle of no less than 15 degrees with the transverse diameter of the spinal cord. The point of the knife should be carried 2 mm. anterior to the emergence of the anterior nerve root.

At upper cervical levels, when the operation is being performed only for pain above the nipple line, the chordotomy incision, 4.5 to 5.5 mm. in depth, may be started 1 mm. in front of the dentate ligament.

Kahn and Rand state that the cervical enlargement is a poor place in which to perform anterolateral chordotomy because of (1) the nearness of the anterior nerve roots to the anterior spinal artery, (2) the danger of injuring important anterior horn cells supplying the upper extremity, and (3) the difficulty with which the cord can be rotated here.

ALPERS, Philadelphia.

Psychiatry and Psychopathology

KORSAKOFF'S PSYCHOSIS ASSOCIATED WITH CEREBRAL TUMORS. B. E. SPROFKIN, and D. SCIARRA, Neurology **2**:427 (Sept.-Oct.) 1952.

Sprofkin and Sciarra describe three cases of the Korsakoff psychosis in patients with brain tumor. Two of these patients had proved cerebral gliomas with diffuse midline involvement. The third patient had a tumor in the posterior portion of the third ventricle. Close questioning of relatives and employers elecited no history of alcoholism in any case.

In a survey of the literature on brain tumors associated with the Korsakoff psychosis, it is interesting to note that the cases reviewed were largely those of tumors in the region of the hypothalamus and that several authors stressed the possible role of the corpora mamillaria in the pathogenesis of the Korsakoff psychosis. In the first case presented in this paper, the mamillary bodies were not involved, but in the second case invasion by neoplastic tissue was noted microscopically. All three cases were characterized by extensive neoplastic involvement of midline structures, including those in the neighborhood of the hypothalamus. The one striking similarity between the cases reported here and those in the literature is the midline location of the tumors.

Several authors have stressed the importance of underlying personality traits in the evolution of the Korsakoff psychosis. Sprofkin and Sciarra suggest that extensive involvement of the deeply situated midline structures and an underlying personality factor may be the main determinants in the development of a Korsakoff psychosis in patients with brain tumors.

ALPERS, Philadelphia.

Meninges and Blood Vessels

MÉNIÈRE'S SYNDROME AS A PREMONITORY SYMPTOM OF CEREBROSPINAL VASCULAR OCCLUSION. W. G. ENSIGN, Ann. Int. Med. **36**:1167 (May) 1952.

Two cases are presented in which the initial clinical picture was indistinguishable from Ménière's syndrome but in which further developments proved the presence of an occlusion of the posterior inferior cerebellar artery. In the first case, that of a man aged 67, Ménière's syndrome was present for six days before the onset of signs of an occlusion. The patient eventually recovered completely. In the second case, that of a woman aged 59, Ménière's syndrome was present two weeks before the signs of arterial occlusion were evident. The patient died.

Although vertigo is considered one of the common and early symptoms of occlusion of the posterior inferior cerebellar artery, the final diagnosis in these two cases was obscured by the presence of the vertigo for so long before the other signs and symptoms made their appearance. Before the onset of the neurologic syndrome a diagnosis of Ménière's syndrome was most likely in each case.

Ensign points out that when presented with a patient with Ménière-like symptoms, one should be constantly alert to the appearance of other symptoms which might point to a more serious underlying disease. One should watch carefully for the appearance of paralyses of the vocal cord, tongue, and soft palate; Horner's syndrome, and sensory changes in any elderly person with Ménière's syndrome.

ALPERS, Philadelphia.

EXTRADURAL HEMATOMAS OF THE POSTERIOR FOSSA. L. J. LEMMEN and R. C. SCHNEIDER, J. Neurosurg. **9**:245 (May) 1952.

Extradural hematoma of the posterior fossa is a rare clinical entity. In a study of several large series of head injuries, the lesions limited to the posterior fossa were found to have an incidence of 0.5% of all extradural hemorrhages. In the presence of a supratentorial lesion, the existence of an extradural lesion in the posterior fossa may not be recognized because of a paucity of clinical findings. Nystagmus, hypotonia, hyporeflexia, cerebellar fits, and cranial nerve abnormality may be of great value in localizing the lesion of the posterior fossa, but too often these signs are masked by concurrent supratentorial lesions. Intracranial decompression by cerebrospinal-fluid otorrhea may minimize the signs of increasing intracranial pressure so that the presence of an epidural hematoma of the posterior fossa may not be recognized. A survey of the literature shows that no one definite clinical picture is common to all. The single important factor in making the diagnosis of the extradural hematoma of the posterior fossa is the high index of suspicion that such a lesion may exist.

In this report are three cases added to the literature, in one of which the lesion, as nearly as could be ascertained, was limited to the posterior fossa. The other two cases, with supratentorial hemorrhage, illustrate the wide variety of clinical signs and symptoms encountered with patients who also harbor an epidural hematoma of the posterior fossa.

The prognosis in extradural hematoma of the posterior fossa is favorable if the condition is recognized early. The cases reported in the literature indicate that the patient has an excellent chance of recovery if prompt evacuation of the extradural clot is performed. This was true in the present series, since all patients made complete recoveries and are well.

ALPERS, Philadelphia.

SUBARACHNOID HEMORRHAGE AS A CAUSE OF SUDDEN DEATH. W. M. TUCKER and B. J. ALPERS, Neurology **2**:203 (May and June) 1952.

Subarachnoid hemorrhage may, on rare occasions, be a cause of sudden death, without accompanying cerebral or ventricular hemorrhage. This fact, not generally recognized, serves to impress the seriousness of outlook in some cases of subarachnoid hemorrhage and, at the same time, raises the question of the cause of death in fatal cases.

Tucker and Alpers report two fatal cases of verified subarachnoid hemorrhage. The first was that of a man aged 54 who suddenly fell to the flood unconscious while straining at stool. In 35 minutes he was dead. Autopsy revealed an extensive subarachnoid hemorrhage at the base of the brain, which became much thinner over the cerebral hemisphere. A small aneurysm was found on the anterior communicating artery, and a well-pronounced foraminal herniation was present. No other cause of death was found.

The second case was that of a woman aged 58 who had evidence of cerebral aneurysm for two weeks before admission to the hospital. Three days after admission she suddenly had a severe headache and generalized convulsion, became unconscious, and died 25 minutes later. Autopsy revealed extensive subarachnoid hemorrhage over the base of the brain, due to a ruptured aneurysm of the right posterior communicating artery. There were no gross hemorrhages anywhere in the brain. No foraminal herniation was disclosed.

The cause of sudden death in subarachnoid hemorrhage is not clear. In the first case here reported, an extensive foraminal herniation explained the sudden death as a consequence of respiratory paralysis. No such mechanism was found in the second case. The amount of bleeding and the associated cerebral edema did not in themselves appear to account for the sudden death, since they occur with equal severity in cerebral and in ventricular hemorrhage, neither of which is a cause of sudden death.

ALPERS, Philadelphia.

Diseases of the Brain

NEUROBLASTOMA WITH SKELETAL METASTASES AND APPARENT RECOVERY. O. W. ANDERSON, A. M. A. Am. J. Dis. Child. **83**:782 (June) 1952.

Neuroblastoma is a malignant tumor, primarily of infancy and early childhood. Ordinarily, this tumor grows rapidly, metastasizes widely and early, and is soon fatal. The average duration of life after diagnosis is less than six months. That this tumor is not invariably fatal is shown by the recent review of 475 reported cases, by Beck and Howard, for which a rate of cures of 10% is recorded. The majority of the patients who have been reported as cured have had complete or partial surgical excision of the original tumor and/or x-ray therapy. Wittenborg, in 1950, reported on 73 patients treated with x-rays, with 22 surviving three or more years. Of this group, there were no survivals among patients with skeletal metastases. Goldring, in 1951, has reported the only case of such a survival. His patient had an inoperable abdominal tumor, with definite metastasis to the liver and probable involvement of the skeletal system. The child received x-ray treatment to the site of the tumor and involved area of the liver, and he recovered. The apparent skeletal involvement seemingly disappeared spontaneously.

Anderson describes the case of a child who, at 7 months of age, was found to have a large, well-circumscribed mass in the left upper portion of the abdomen. The child had no complaints and was normally developed. At operation a well-encapsulated tumor of the left adrenal gland, the size of a grapefruit, was removed. The pathologist's diagnosis, confirmed by a second opinion, was neuroblastoma.

After an uneventful postoperative course, survey roentgenograms of the entire skeleton were made and revealed nothing abnormal. About six weeks after operation the child seemed to have pain in the right leg, and roentgenograms showed changes in the right femur, believed to be metastatic neuroblastoma. A month later the left leg was painful, necessitating daily administration of codeine. Roentgenograms taken a month later showed destructive processes advanced in both femurs. At this time a course of corticotropin therapy was instituted, consisting of 50 mg. daily for four days and 40 mg. daily for six days longer. As no change was noted, therapy was stopped.

The patient continued to need codeine for two months longer, and then gradual improvement started. He needed no codeine and became more active. At 20 months of age he was well and walking freely. Another set of roentgenograms of the femurs, taken at the age of 21½ months, showed them to be entirely normal.

Anderson draws no conclusions as to what part the corticotropin treatment played in the change which took place in this child.

ALPERS, Philadelphia.

TRAUMATIC BRAIN-STEM THROMBOSIS. E. C. KUNKLE, J. C. MULLER, and G. L. ODOM, Ann. Int. Med. **36**:1329 (May) 1952.

The authors present the only reported case of survival from an uncommon accident—injury to the brain stem following vigorous chiropractic manipulation of the head and neck. The patient, a man aged 35 suffering from rheumatoid arthritis and unproved gout, had received a course of chiropractic treatments for three weeks for alleviaton of severe headaches, which had been present for five weeks. The sixth, and final, adjustment was unusually vigorous, involving stretching and rotary movement of the neck and then firm pressure on the right side of the neck.

The resulting neurologic syndrome described is attributable to infarction of the lateral medullary plate secondary to thrombosis of the ipsilateral vertebral artery or one of its branches. The patient survived, with disabling residua.

Pratt-Thomas and Berger previously described two cases of rapidly fatal thrombosis of a vertebral artery or its branches in young adults, in each instance apparently precipitated by chiropractic treatment applied to the neck. The injury to the brain stem in these three cases is presumably related to traumatic occlusion of a vertebral artery, for past experimental studies have demonstrated a peculiar vulnerability of this vessel to compression when the head is overextended and flexed to the opposite side.

ALPERS, Philadelphia.

HEMIPLEGIA DURING TETRAETHYLTHIURAM DISULFIDE (ANTABUSE) [DISULFIRAM] THERAPY. W. M. JOHNSON, J. A. M. A. **149**:1014 (July 12) 1952.

Johnson reports the development of hemiplegia after the fifth dose of disulfiram was given in the treatment of an alcoholic. The patient, a woman of 49, was a periodic drinker and was considered a true psychopath. She was admitted at this time with a history of having been drinking heavily for four or five days.

The patient was a well-nourished woman with a blood pressure of 160 systolic and 82 diastolic. The eyegrounds were normal, and there were no abnormal physical findings. Urinalysis, blood chemistry determinations, and liver function tests all gave essentially normal results. Roentgenograms of the heart, aorta, and lungs revealed nothing abnormal.

A dose of 1 gm. of disulfiram was given at bedtime on four successive nights. The following morning a trial dose of 10 cc. of whiskey was given. There were moderate facial flushing, a slight increase in the pulse rate, and a very slight drop in blood pressure. The fifth dose was given that night. The following morning she complained of a severe headache, and within a few hours presented the typical picture of a cerebrovascular accident, with right hemiplegia. Her blood pressure was 220 systolic and 120 diastolic. After a left stellate ganglion block, papaverine hydrochloride, and injections of 50% magnesium sulfate, the patient showed rapid improvement. She was discharged 12 days after the occurrence of the cerebrovascular accident with a normal blood pressure (110 to 140 systolic and 70 to 90 diastolic); she was able to walk without difficulty and to use her right arm fairly, but she was still unable to write with the right hand.

Johnson states it is possible that this cerebral accident was merely coincidental to the use of the drug, and not attributable to it. He reports it in order that anyone using the drug may be aware of the possibility of such a complication.

ALPERS, Philadelphia.

INTRACRANIAL TUBERCULOMAS. R. A. GONZALES, J. Neurosurg. **9**:555 (Nov.) 1952.

Before the advent of streptomycin, the surgical treatment of cerebral tuberculoma was discouraging because of the common occurrence of postoperative tuberculous meningitis. In this paper, the experiences encountered in 10 consecutive cases of verified intracranial tuberculomas are recorded. In all 10 cases an operation was carired out. Three patients died and seven survived. The seven survivors were followed from 12 to 36 months, and all were living and well at the time of this report.

The author reviews the incidence, symptoms, and operative findings in this series and draws the following conclusions: Tuberculoma is a common intracranial lesion. It is more prevalent in the first two decades of life. The duration of symptoms may be from 2 to 35 months. A history of fever at the onset of symptoms may be obtained. Headache and early signs of increased intracranial pressure are the commonest clinical features. The waterlogged, glossy appearance of the surrounding brain may help in the gross diagnosis of the lesion at the operating table. Complete surgical removal of the lesion, whenever feasible, combined with adequate streptomycin therapy should be the therapeutic method of choice. Children seem to have a better chance of survival than adults.

The three patients who died were adults. For one a diagnosis of intrapontile glioma was made, but craniectomy in the left suboccipital area did not disclose a tumor at the angle. The patient was subjected to intensive x-ray therapy but died three months later, of the effects of inracranial hypertension. Autopsy revealed a sausage-shaped tuberculoma, which extended from the left cerebellar lobe to the pons, midbrain, cerebral peduncle, and thalamus on the left side. The other two postoperative deaths were from tuberculous meningitis. Both patients were Indians; they had the longest duration of symptoms, were hemiplegic and extremely emaciated on admission, and had the largest tumors. Both were given dihydrostreptomycin, and one had additional intravenous injections of glucosulfone sodium (Promin). One died 87 days, and the other 101 days, after operation.

ALPERS, Philadelphia.

CEREBRAL ANGIOGRAPHY IN DIAGNOSIS OF SUBDURAL HEMATOMA. J. M. STEIN, Neurology **2**:389 (Sept.) 1952.

Fifteen patients suspected of subdural hematoma, in the presence of other major conditions and problems of differential diagnosis, were studied by percutaneous cerebral angiography.

Seven patients had verified subdural hematomas. In six of them the angiogram revealed a specific pattern. The film for the seventh was unsatisfactory because of motion, but a mass could be diagnosed, nevertheless. Of the remaining eight patients, angiography revealed a verified neoplasm in one and an intracerebral mass verified as a chronic intracerebral abscess in another. Five others, with normal angiograms, recovered, with subsequent pneumoencephalograms all negative for mass lesions. Another patient with a normal angiogram died of a verified cerebral laceration.

Stein proposes cerebral angiography as a method for the specific diagnosis of subdural hematomas. With its use, needless surgery can be avoided. In addition, it has the advantage of better localization of intracerebral masses and sometimes better definition of their nature.

ALPERS, Philadelphia.

ROLE OF FOOD ALLERGY IN MULTIPLE SCLEROSIS. O. F. EHRENTHEIL, M. H. SCHULMAN, and L. ALEXANDER, Neurology **2**:412 (Sept.) 1952.

This study was undertaken in an effort to obtain answers to the following questions: 1. How often does food allergy occur in patients with multiple sclerosis? 2. Which foods are most commonly involved in the sensitivity of the patient with multiple sclerosis? 3. Do patients with multiple sclerosis benefit when placed on a diet from which all reacting foods have been eliminated? 4. Does reintroduction of the eliminated food produce any reaction?

In a series of 67 clinically proved cases of multiple sclerosis the following routine was adopted: (1) a thorough allergic history on a standardized form; (2) a complete dietary analysis of each patient's food intake on a standardized form; (3) an examination of each patient's nasal mucous membrane; (4) skin testing by the scratch method with 15 common foods, plus mixed tree, mixed grass, and ragweed pollen extracts; (5) ophthalmic tests with 25 common foods.

The authors found that ophthalmic tests with 25 food proteins in these cases gave a very high percentage of positive reactions to rye and wheat. This finding proved statistically to be significantly higher than in the random population.

Allergen-free diets based on a carefully taken allergic history and on the results of ophthalmic tests brought about favorable results in 31% of the cases. In 12 cases the temporary reintroduction of the previously omitted food resulted in a temporary exacerbation of symptoms.

It was found that symptoms which are not necessarily related to, but frequently associated with, multiple sclerosis, such as constipation, headaches, nausea, general fatigue, and urinary frequency, were often alleviated.

An analysis of the dietary habits of a representative group of patients with multiple sclerosis showed lack in calcium and iron in 50% of the cases, lack of fat in 24%, lack of protein in 31%, and lack of carbohydrate in only 8.9%.

ALPERS, Philadelphia.

ASTROCYTOMA OF THE PONS WITH LONG SURVIVAL AND ULTIMATE VENTRICULOMASTOIDOSTOMY. H. W. DODGE JR., R. H. MILLER, C. F. LAKE, and W. M. CRAIG, Proc. Staff Meet., Mayo Clin. **27**:219 (May 21) 1952.

A tumor of the pons commonly belongs to the group of gliomas and usually is a member of the series of astrocytomas. Children are most commonly affected. The usual survival period from onset of symptoms is three years or less. Partially responsible for the patient's early death is the close proximity of the tumor to the cerebral aqueduct, the fourth ventricle, the long nerve pathways, and the vital nuclei of the brain stem. In addition, the infiltrating nature of the glioma and its surgical inaccessibility provide a gloomy outlook.

The authors present the case of a young woman who in 1937, at the age of 17, underwent subtotal removal of an astrocytoma, Grade 2, of the pons. She was seen again in 1944, complaining of headaches and incoordination of her left side, of increasing severity. Roentgen therapy alleviated the acute symptoms, and another course of x-rays was administered two months later. The patient felt well and lived a comparatively normal life until July, 1950, or about 13 years after the original operation. Then nausea, loss of appetite, gagging, and blurred vision occurred. Since these symptoms increased and hiccup appeared six months later, she returned for advice. The optic fundi were normal. There was weakness of the left side of the tongue, and the left vocal cord was fixed. Raduim therapy was administered to the pontine region, after which the patient's condition improved.

Three months later, diplopia reappeared, and she showed bilateral acute papilledema of 4 D. Since the signs of acute obstructive hydrocephalus had developed, it was decided to relieve the hydrocephalus and not attempt to relieve the obstruction to the aqueduct of Sylvius, which presumably was being brought about by growth of the tumor. With use of thiopental (pentothal) anesthesia, the left mastoid (tympanic) antrum was entered. Then, by means of polyethylene tube, a communication between the posterior horn of the left lateral ventricle and the left mastoid antrum was established under the scalp.

The patient was dismissed to her home on the 10th postoperative day. Except for a few days when she had a severe infection of the upper respiratory tract, she experienced a completely satisfactory convalescence. When she was seen six months later, the shunt was working well, the previous papilledema had disappeared except for slight fullness of the upper poles of the optic discs, and there was a conduction type of deafness, Grade 1, in the left ear.

The authors point out that through the combined efforts of those engaged in neurosurgery, neuroradiology, neurology, and otolaryngology, this woman is able to live a useful, active, comfortable life, 14 years after her original operation.

ALPERS, Philadelphia.

Posterior Fossa Dermoid Cysts with Special Reference to Intracranial Infection. V. Logue and K. Till, J. Neurol., Neurosurg. & Psychiat. **15**:1 (Feb.) 1952.

A study of 32 cases of the dermoid cyst of the posterior fossa demonstrated that four clinical types can be recognized, the differentiation depending on their anatomical situation and the presence or absence of an occipital dermal sinus. These types are (1) extradural dermoid cyst with complete dermal sinus, (2) intradural dermoid cyst without dermal sinus, (3) intradural dermoid with incomplete dermal sinus, and (4) intradermal dermoid with complete dermal sinus. The characteristic features of each type and their roentgenographic appearance are described.

Attention is drawn to the ease with which infection can enter the skull to cause meningitis or abscess, in particular in the case of the intradural dermoid cyst with a complete dermal sinus.

These tumors obviously carry a serious risk, whatever type of treatment is adopted, whether it be early excision, as a prophylactic measure against infection, or removal delayed until intracranial spread of sepsis has occurred. Although it may seem a drastic procedure to subject an infant or a young child to a major intracranial operation when its only apparent disability is a discharging occipital sinus, the occurrence of serious inflammatory complications is inevitable; and the authors believe that removal of the tumor, once the diagnosis has been made, and before septic complications occur, is the least dangerous method. Postoperative meningitis may be anticipated, and perhaps prevented, by a full therapeutic course of the indicated antibiotic.

Although dermoid cyst of the posterior fossa is an uncommon tumor, its possibility should be borne in mind when one is treating any infant or young child with symptoms of an abscess in the posterior fossa situated in the midline, or meningitis which is resistant to, or relapses in spite of, adequate treatment, particularly if it is due to the coliform group of organisms.

Alpers, Philadelphia.

Wounds of the Visual Pathway: II. The Striate Cortex. J. M. K. Spalding, J. Neurol., Neurosurg. & Psychiat. **15**:169 (Aug.) 1952.

This paper reports some of the visual field defects which occur in gunshot wounds of the striate cortex, with particular reference to the anatomical deductions which may be made from them.

Spalding reviewed a series of 958 cases of penetrating head injury, mainly gunshot wounds, to determine what light they might throw on the anatomy of the striate cortex (Area 17). In 188 of these cases there was a visual field defect attributable to injury to the visual radiation or the striate cortex. In 72 cases the injury affected primarily the striate cortex, and several characteristic instances are presented and discussed.

In this survey, Spalding finds that central ("macular") vision is represented unilaterally. The horizontal meridian of the visual field is represented in the floor of the calcarine fissure.

The extent of striate cortex devoted to central vision is defined. Central vision within the 8- to 10-degree circumference (i. e., macular vision) is represented on that part of the striate cortex which faces posteriorly or posteromedially. The remainder, which faces medially, represents vision more peripheral than 10 degrees from the fixation point.

The lips of the calcarine fissure at the point where the striate cortex on the medial surface of the hemisphere becomes continuous with that on the posteromedial surface represent the points 8 degrees from the fixation point and 30 degrees from the vertical meridian.

Alpers, Philadelphia.

Diseases of the Spinal Cord

Occurrence of Poliomyelitis in Relation to Tonsillectomies at Various Intervals. F. H. Top, J. A. M. A. **150**:534 (Oct. 11) 1952.

Studies on the relationship between tonsillectomies and poliomyelitis have been concerned principally with the occurrence of the disease within a month of the surgical procedure. Many investigators are of the opinion that poliomyelitis occurs more frequently after recent tonsillectomy than normally would be expected and that when it develops it is likely to result in a severer clinical type (bulbar or spinobulbar) if tonsillectomy has preceded an attack of the disease within 30 days.

The Detroit study, made in 1939, did not substantiate the finding of increased risk of tonsillectomy during a period of one month prior to an attack of the disease, but it did demonstrate the likelihood that a severer type of disease would develop. The present study is a survey of the tonsillectomy status of patients admitted to the Herman Keifer Hospital during the period from 1940 to 1949, and does no include the 1939 experience.

During the 1940-1949 decade, 1,947 patients who had had poliomyelitis were discharged from the hospital. Of this group, 1,011 patients gave a history, and on examination showed evidence, of removal of the tonsils. The proportion having undergone tonsillectomy was 51.9%.

High percentages of patients who had had tonsillectomy had the bulbar or spinobulbar type of poliomyelitis. The rates for these types were 85.1 and 68.7%, respectively, as compared with 45.6% for the nonparalytic type and 43.1% for the spinal type. The fatality rate of 93.5% for the bulbar type when tonsils had been removed was still more striking and was in marked contrast to that for the spinobulbar type (56.9%).

The time elapsed between tonsillectomy and an attack of poliomyelitis was studied. The proportion of patients with a history of tonsillectomy within one month of an attack was only 2.1%, and that for a period of less than one year was 8.3%.

These data are challenging in their implications and call for sober judgment with regard to the desirability of removal of tonsils except when there are excellent clinical indications. The data here presented are strongly suggestive that there is a greater chance of a severe form or of a fatal termination if tonsils have been removed at sometime prior to an attack of poliomyelitis.

ALPERS, Philadelphia.

Peripheral and Cranial Nerves

BELL'S PALSY. R. C. MARTIN, A. M. A. Arch. Otolaryng. **55**:405 (April) 1952.

The term Bell's palsy denotes facial paresis occurring suddenly in an otherwise healthy person. The prognosis of recovery must be based on a careful history that notes the type of onset, the physical findings, and the results of special tests. Onset may be sudden, gradual, and/or accompanied with pain. The presence of pain gives a poorer prognosis. The physical findings should take into account muscular tone, voluntary control, emotional control, loss of taste, and tearing. There is a wide variance of opinion as to the value of the faradic stimulation test and of electromyography.

The condition is a neuritis. It is occasionally due to infection in the teeth, throat, or nose. Any foci about these structures should be cleaned up. Findlay has stated that patients exhibiting symptoms of such infection have a more gradual onset, without pain, and consequently the best prognosis.

Other workers have experimentally established the ischemic nature of Bell's palsy. Hilger believes the primary disturbance is of the vasa nervorum. Surgery corrects the resulting edema, but not the vascular disturbance that is the underlying cause. It is therefore recommended that medical therapy, i. e., intravenous injection of procaine hydrochloride, intravenous injection of nicotinic acid, muscle support, and galvanic muscle stimulation should be tried first. The proportion of patients who fail to recover varies considerably, but is given as 15 to 25%. Kettel suggests that if after two months there is no return of function with medical therapy or if there is a relapsing paresis, surgical treatment may be done. The author believes more nerves will be saved by medical therapy than by perhaps unnecessary surgery.

ALPERS, Philadelphia.

SUMMATION OF PAPERS ON MANAGEMENT OF FACIAL PARALYSIS. S. BUNNELL, A. M. A. Arch. Otolaryng. **55**:417 (April) 1952.

The facial nerve is unique in that it is enclosed from the geniculate ganglion to the stylomastoid foramen in a close-fitting tunnel. Therefore any traumatism, such as exposure to heat or to cold, causes the nerve to swell. The swelling of the nerve in the closed tunnel squeezes out its own blood supply, thus resulting first in ischemia, then in necrosis, and, finally, in fibrosis. Therefore, Bunnell points out, the only possible time for prophylaxis or prevention of Bell's palsy is during the first few hours—three hours if the blockage of circulation is complete, but a

few more if partial. Prompt decompression will keep the nerve alive. If decompression is not done, the ischemia will result in a degree of damage to the nerve, ranging from temporary palsy to permanent paralysis.

Prompt surgical decompression will be unnecessary in 80% of cases. In the other 20%, or worst cases, decompression should be done at once. Unfortunately, there is no solution to the problem of recognizing and actually preventing the condition in the 20% of cases in which palsy will inevitably develop. The author states that it is probably best to decompress on loss of faradic response through nerve and when other signs indicate that the paralysis is severe, but this is too late to prevent necrosis of the nerve.

Signs of partial nerve damage or recovery are practically the same. It is best in evaluating to use all tests and signs. Bunnell feels that electromyography is 90% reliable in the hands of a careful operator. Electrical tests are useful to determine the state of the nerve, the prognosis, and whether or not the muscles will react if the nerve is regained.

The author reviews the operative procedures and recommends postoperative muscle stimulation and relaxation. Failing repair of the nerve, plastic surgery is advisable.

ALPERS, Philadelphia.

HYPERTROPHIC SPINAL PACHYMENINGITIS. P. C. BUCY and L. W. FREEMAN, J. Neurosurg. **9**:564 (Nov.) 1952.

The authors review the literature on hypertrophic spinal pachymeningitis since the original description by Charcot and Joffray. They deplore the general belief that this disease is of syphilitic origin and that invaluable time is frequently lost in administering antisyphilitic treatment in the absence of positive evidence of syphilis. It must be remembered that with progression of the disease the dura mater may become densely adherent to the leptomeninges and the spinal cord, making satisfactory separation impossible or very difficult, and that eventually changes within the spinal cord, e. g., softenings and cystic degenerations, may become irremediable.

In this paper, the authors report two cases of hypertrophic spinal pachymeningitis, the cervical region being involved in one and the upper thoracic region in the other. In both cases operation was performed, and all the grossly thickened dura mater lying posterior to the points of emergence of the spinal nerve roots was removed. In both there was a dramatic recovery from severe spastic paraplegia. The recovery from the atrophic weakness of the upper extremities in the case of the cervical lesion was also dramatic. In both instances the recoveries have been maintained for many years.

A study of these cases and of the literature reveals a rather constant clinical picture and the fact that in the majority of cases there is no known etiological factor. There is no known form of useful treatment except the surgical excision of the hypertrophic dura mater that is compressing the nervous system.

ALPERS, Philadelphia.

DYSPHASIA IN LEFT-HANDED PATIENTS WITH UNILATERAL BRAIN LESIONS. M. E. HUMPHREY, and O. L. ZANGWILL, J. Neurol., Neurosurg. & Psychiat. **15**:184 (Aug.) 1952.

Humphrey and Zangwill studied the histories of approximately 1,150 cases of penetrating brain wounds from World War II. The studies were made from the point of view of psychological functions in general, but especially with reference to handedness and the difference in effects of left- and right-sided cerebral lesions, particularly on the various manifestations of dysphasia.

Ten carefully selected cases of unilateral brain lesion (five on the left side and five on the right side) in naturally left-handed patients of good intelligence were studied with reference to the cerebral representation of language functions. It was found that dysphasia was present in all cases of lesion of the left hemisphere and in all but one case of lesion of the right hemisphere. With respect to balance the dysphasic symptoms were severer in the former group, although defects of calculation were more prominent in the latter.

The authors discuss the theoretical implications of their findings in regard to handedness and cerebral dominance. The fact which emerged most clearly from this study of the effects of

unilateral cerebral lesions in left-handed patients was that some evidence of "language disorder" was found in one form or another in all cases except one, irrespective of the laterality of the lesion. The importance of obtaining accurate information as to handedness in the course of routine neurological examination of patients with brain injury is stressed. Further research concerning the cerebral organization that is associated with left-handedness is indicated.

ALPERS, Philadelphia.

Treatment, Neurosurgery

TREATMENT OF HEMOPHILUS INFLUENZAE MENINGITIS. M. H. LEPPER, P. F. WEHRLE, and N. BLATT, A. M. A. Am. J. Dis. Child. **83**:763 (June) 1952.

Eighteen patients with meningitis due to Hemophilus influenzae were treated with aureomycin alone, and 14 patients, with a combination of aureomycin, streptomycin, and sulfisoxazole (Gantrisin). When aureomycin was given intravenously in doses of 50 mg. per kilogram every 24 hours, results were as good, as regards duration of fever, pleocytosis spinalis, and complications, as when the combination was used.

In two patients penicillin in doses of 1,000,000 units intramuscularly every two hours was used, with success. One patient, not in these series, who had the encephalitic form of the disease, died in spite of treatment with aureomycin, penicillin, and sulfisoxazole. Three patients with subdural effusions were treated successfully by repeated aspiration.

Lepper and his colleagues conclude that aureomycin used alone is a successful therapeutic agent in meningitis due to H. influenzae and that no additional advantage is gained by using streptomycin and sulfisoxazole in addition.

ALPERS, Philadelphia.

TREATMENT OF BACTERIAL MENINGITIS OF UNUSUAL ETIOLOGY AND PURULENT MENINGITIS OF UNKNOWN ORIGIN. M. H. LEPPER, N. H. BLATT, P. F. WEHRLE, and H. W. SPIES, A. M. A. Am. J. Dis. Child. **85**:295 (March) 1953.

The authors report 21 cases of meningitis due to specific etiologic agents, including green-producing (α) and hemolytic (β) Streptococcus, Staphylococcus, Escherichia coli, Klebsiella pneumoniae, Alcaligenes, Corynebacterium, Pseudomonas, and Listeria. Twenty other cases of purulent meningitis in which the etiologic agent could not be found are also included. In a large number of patients with meningitis an exact etiologic diagnosis cannot be made before therapy is started. Penicillin was satisfactory for most of the coccal infections and most of the infections of unknown cause. Aureomycin, oxytetracycline (Terramycin), chloramphenicol, and polymyxin are recommended in the infections with the Gram-negative bacilli. In patients without demonstrable organisms in a purulent spinal fluid the age and degree of illness should govern the choice of therapy. In children under 10 years of age Hemophilus influenzae is the commonest organism, and so one of the drugs used for infections with Gram-negative bacilli is suggested. If the child is critically ill and a pneumococcal infection is suspected, penicillin should be used, and streptomycin may be added for the influenza bacillus. In patients over 10 years the Pneumococcus is the most serious infection agent and penicillin should be used, with streptomycin added when the patient is critically ill. If cultures establish the diagnosis later, appropriate changes in treatment can be made.

SIEKERT, Rochester, Minn.

SOME VIEWPOINTS ON THE OPERATIVE TREATMENT IN MÉNIÈRE'S DISEASE. P. FRENCKNER, A. M. A. Arch. Otolaryng. **55**:420 (April) 1952.

Most authors agree that the symptoms of Ménière's disease are probably caused by an increase in pressure on the labyrinth. Etiologic factors may be allergy, disturbances in histamine conversion, hypovitaminosis C, and vasospasm, accompanied with increased capillary permeability. As the etiology and pathology are not sufficiently well known, it is obvious that a single therapeutic principle could not be adequate. In this paper, the author offers an addition to and modification of the operative procedure in Ménière's disease. The conservative methods are discussed only as far as they are important as preliminary or supplementary aids to the surgical treatment.

Operative methods used earlier, which consisted either of cutting the vestibular nerve or of destructive operations on the labyrinth, usually resulted in relief of the vertigo, but not in decrease of the tinnitus. In addition, the labyrinthine operations were intended to destroy the existent hearing. The operative method reported in this paper by Frenckner is intended to eliminate the vertigo and tinnitus, or at least to diminish them to the point of freedom from discomfort, and to protect the residual hearing as well. This is achieved by means of (1) relief of the intralabyrinthine pressure through fenestration, (2) abolition of the vestibular function through tamponade of the vestibule, and (3) an attempt to affect tinnitus through tympanosympathectomy and cutting of the chorda tympani nerve, the tendon of the tensor tympani muscle, and the tendon of the stapedius muscle.

The cases in which operation was performed (13 in number) comprise an experimental series of the most serious which could be procured. All patients had been practically invalidated by their disease. The results were completely satisfactory in respect to vertigo and tinnitus. Hearing could be retained in most cases, although it deteriorated somewhat as a result of the operation.

In later cases, not belonging to this series, the technique has been changed. Both fenestration and tympanosympathectomy have been performed without disturbing the ossicle chain, and it is hoped the hearing may be preserved without further loss.

ALPERS, Philadelphia.

SCIATIC AND FEMORAL NERVE BLOCK. D. C. MOORE, J. A. M. A. **150**:550 (Oct. 11) 1952.

Moore points out that the combination of sciatic and femoral nerve block is one of the most useful, yet most neglected, of anesthetic procedures. In this paper he describes an effective technique for such block that has given a satisfactory block in 90% of 805 cases. The advantages of this combined block are enumerated and compared with those of spinal and general anesthesia.

Tetracaine (Pontocaine) hydrochloride is his choice of anesthetic agent because toxic reactions are relatively infrequent and it produces an anesthesia that lasts four to six hours, with solutions containing epinephrine giving longer durations.

The results obtained in this series of cases seem to justify the belief that this combined block is an entirely satisfactory form of anesthesia for operations on and manipulations of the leg and foot from 2 in. (5 cm.) below the patella down.

ALPERS, Philadelphia.

BETAINE AND GLYCOCYAMINE THERAPY FOR THE CHRONIC RESIDUALS OF POLIOMYELITIS. B. D. FALLIS and R. L. LAM, J. A. M. A. **150**:851 (Nov. 1) 1952.

Beneficial results from the feeding of creatine precursors have been reported in cases in which muscles have been affected in poliomyelitis. In patients who had suffered disabilities of poliomyelitis, Borsook, Billig, and Golseth reported, in addition to a sense of well-being, lessening of fatigue, and greater strength and endurance, a substantial increase in motor unit activity recorded electromyographically during the first three weeks of therapy if the muscles had demonstrated residual function in the pretreatment assay. A significant increment in power was found to occur in the two months following this initial period.

Fallis and Lam tested 57 patients, aged 2 to 46 years, presenting various degrees and distributions of motor impairment as poliomyelitic residuals, for the effect of betaine-glycocyamine feeding on improvement in muscle status. Under intensive physical therapy by approved methods, all had reached a plateau. The group was divided into two samples, one, of 35 patients, receiving betaine and glycocyanine and the other, of 22 patients, receiving placebos.

Seven patients discontinued treatment in the early weeks because they noted no improvement; five of these were receiving betaine and glycocyamine, and two placebos. Of the remainder, 20 patients were carried an average of 6.6 weeks on placebos, and 30, an average of 8.1 weeks on betaine-glycocyamine therapy. The percentage of patients who claimed improvement and in whom manipulative testing might show a minor increase in strength over the pretreatment status was approximately the same for the two groups. The betaine-glycocyamine group showed a significantly higher incidence of urinary frequency, related presumably to higher values for creatine excretion.

These findings are at variance with those reported by Borsook, Billig, and Golseth.

ALPERS, Philadelphia.

SURGICAL TREATMENT OF INTRACTABLE PHANTOM-LIMB PAIN. MURRAY A. FALCONER, Brit. M. J. **1**:299 (Feb. 7) 1953.

Falconer reports his experience in the treatment of 12 patients with intractable phantom limb pain involving both upper and lower extremities. All patients had complained of the pain for a period of years, and many had been unsuccessfully treated by resection of the stump neuroma, sympathectomy, or reamputation. Anterolateral chordotomy at the appropriate level gave pronounced relief from pain in nine and slight benefit in one patient, but in the remaining two patients the pain returned. Although this type of pain has been reported to have been relieved by such procedures as percussion of stump neuromas, posterior chordotomy, ablation of the postcentral gyrus, and frontal lobotomy, Falconer believes that anterolateral chordotomy gives the best results. He explains the severe pain in phantom limbs on the basis that "the cells of the substantia gelatinosa, cut off from their normal patterned stream of stimuli, discharge spontaneously or react to unusual sources of stimuli, and so provoke pain."

ECHOLS, New Orleans.

MYSOLINE: A NEW DRUG IN THE TREATMENT OF EPILEPSY. R. HANDLEY and A. S. R. STEWART, Lancet **1**:742 (April 12) 1952.

Handley and Stewart report the results of treatment with a new anticonvulsant drug, Mysoline (5-phenyl-5-ethylhexahydropyrimidine-4,6-dione), which is closely related chemically to phenobarbital, in 40 patients in an epileptic colony.

The previous drugs were gradually withdrawn over a two-week period and Mysoline was gradually added, the usual dose of Mysoline being 1 gm. a day. An effective dose up to 1.6 gm. a day gave few side-effects and did not seem to make the patients sleepy. One patient had a morbilliform rash; another complained of slight nausea and abdominal discomfort, and transient feelings of dizziness, listlessness, disturbance of accommodation, and sleepiness were noted. With no patient was it necessary to discontinue use of the drug. Hypertrophy of the gums and abnormal blood changes did not occur.

The drug was studied for its effect on grand mal attacks only. It was found that 80% of patients showed improvement and 30% were completely free from attacks of all kinds. Only one patient was significantly worse. Convulsions which still occurred were often much less severe. The "hang-over" time was less. There was absence of hypnotic effect, and patients reported a feeling of fitness and mental alertness.

MADOW, Philadelphia.

THE ACTION OF DECAMETHONIUM IODIDE (C.10) IN MYASTHENIA GRAVIS. H. C. CHURCHILL-DAVIDSON and A. T. RICHARDSON, J. Neurol., Neurosurg. & Psychiat. **15**:129 (May) 1952.

The abnormal fatigue of the voluntary muscles in myasthenia gravis is due to a progressive failure of conduction at the myoneural junction after muscle contraction. The exact nature of the neuromuscular block remains obscure. Working on muscle relaxation with decamethonium iodide, Paton and Zaimis had found that fundamentally it acts in a way analogous to acetylcholine, that is, to produce depolarization of the muscle surface membrane in the region of the motor end-plate and a contraction of the muscle fibers. In the case of decamethonium iodide, however, the muscle fiber remains in a depolarized state for a prolonged period, in which it is unable to respond to nerve impulses—a condition of neuromuscular block.

In this paper the authors describe the effect of intravenous administration of decamethonium iodide on the muscles of 16 normal control subjects and 11 patients with myasthenia gravis. Their results indicate a generalized tolerance of the muscle fibers of myasthenic patients to decamethonium iodide, particularly in patients in whom the only clinical evidence of myasthenia is ptosis and diplopia. However, when the muscle fatigue is more widespread, the tolerance is more difficult to demonstrate, for, although it is still marked in the unaffected muscles, it is reduced in the muscles affected by the disease. This resistance to the depolarizing action of decamethonium iodide may be due either to the destruction of the compound before it is able to act on the muscle fibers or to an inherent resistance of the end-plate of myasthenic muscle fibers to its action.

ALPERS, Philadelphia.

OBSERVATIONS ON PARTIAL REMOVAL OF THE POST-CENTRAL GYRUS FOR PAIN. W. LEWIN and C. G. PHILLIPS, J. Neurol., Neurosurg. & Psychiat. **15**:143 (Aug.) 1952.

Lewin and Phillips record three cases in which partial resection of the postcentral gyrus was undertaken for the relief of pain. In the first patient the pain developed during an unusual prolonged sensory painful aura in traumatic epilepsy; the second patient had intractable pain in a phantom foot, and the third had a painful thigh stump. In all three patients electrical stimulation of the appropriate area of the postcentral gyrus reduced the pain complained of by the patient, and relief followed the removal of this area of cortex.

Whether removal of these small areas of sensory cortex will permanently relieve pain is still undecided. The attraction of such an operation is the possibility of relieving pain without producing any marked permanent motor or sensory deficit or personality change. The possible sequel is the production of epilepsy, but so far there is no record of this complication. If further experience is favorable, the place of the operation in treatment will have to be considered in relation to alternative operations on the frontal lobes.

ALPERS, Philadelphia.

Encephalography, Ventriculography and Roentgenography

ANTERIOR DISLOCATION OF FIRST CERVICAL VERTEBRA SIMULATING CEREBRAL BIRTH INJURY IN INFANCY. E. ALEXANDER JR., R. MASLAND, and C. HARRIS, A. M. A. Am. J. Dis. Child. **85**:173 (Feb.) 1953.

The authors report the case of a 21-month-old boy who was admitted *in extremis* with a history of episodes of weakness and difficulty in breathing during the preceding 10 months. The pregnancy, delivery, and neonatal period were normal. He had used his left hand less than his right, and his right foot dragged when he walked. During the three months prior to admission his condition had deteriorated. Examination revealed extreme weakness, labored respiration, listlessness, and resistance to flexion of the neck. He was alert and attentive. The reflexes were normal; the toe responses were equivocally extensor; sensation appeared intact. Cervical roentgenograms demonstrated forward displacement of the atlas on the axis. Manometric studies of the cerebrospinal fluid showed a slow response on jugular compression. A filling defect at the first and second cervical levels was seen on myelograms. Suboccipital craniotomy and laminectomy of the first two cervical vertebrae were carried out. The arch of the atlas was displaced 1 to 2 cm. anteriorly, and there was marked constriction of the dura and indentation of the cord beneath. Despite electrophrenic stimulations, the patient died nine hours after operation. Examination showed the odontoid to be completely cartilaginous. The cord was constricted to one-fifth its normal size. There was moderate arachnoidal reaction. Multiple small cysts were present within the substance of the cord.

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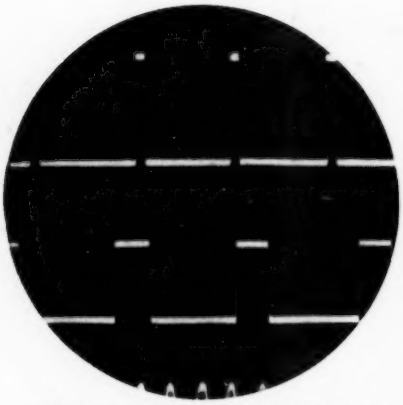

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This instrument is the latest advance in Offner electrotherapy apparatus, and as in all Offner electrotherapy instruments, it features safety for the patient and operator, and accuracy of current control.

Excellent clinical results have been obtained by the many users of the Type 736A, in a wide variety of psychiatric disorders, using the treatment modalities described by Hirschfeld.[1]

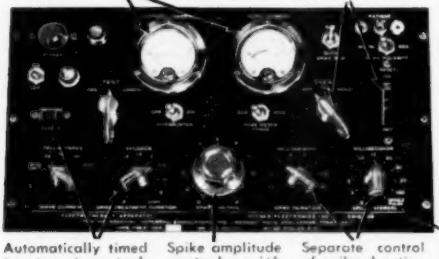
Electrical stimulation is based on the Liberson brief stimulus current, first introduced eight years ago. This allows cerebral stimulation to be achieved with minimum undesired after-effects. While various types of instruments can be used for the purpose, the importance of accuracy of current wave-form and intensity control is clear,[2] in insuring reproducibility of therapeutic results; and only in Offner electrotherapy instruments are all parameters controlled with scientific precision.

The versatility of current control in the Type 736A is such that the one instrument covers the full range of requirements of electrotherapy:

The duration of each current "spike" is adjustable from 0.15 to 2 milliseconds, and their frequency, from 10 to 400 per second.

The peak current is adjustable from zero to 1000 ma, and is accurately metered.

Automatically or manually timed treatments, slow or instantaneous rise, and interrupted currents are available.



1. G. Hirschfeld, *Diseases of the Nervous System* **12**: 3-7 (1951)

2. George Ulett, Proc. of the Electroshock Research Assn., Printed in *Confinia Neurologica* **12**: 298-305 (1952)

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